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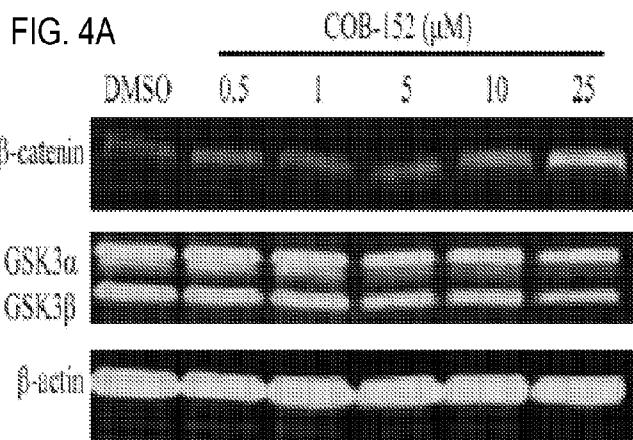
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(54) Title: METHODS AND COMPOSITIONS TO MODIFY GSK-3 ACTIVITY

(57) Abstract: Methods for modulating
GSK-3 activity and methods for treating
a GSK-3 -mediated disorder in a subject
in need thereof. The methods include
contacting a cell expressing GSK-3 with
or administering to the subject in need a
therapeutically effective amount of one
or more compounds of General Formula
(I) or General Formula (II); or pharma-
ceutically-acceptable salts or solvates
thereof.



TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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METHODS AND COMPOSITIONS TO MODIFY GSK-3 ACTIVITY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119 of U.S. Provisional Patent Application No. 62/026,164, filed July 18, 2014, entitled, "Prevention and Treatment of Non-Alcoholic Fatty Liver Disease" (Docket OHU 2034 M2/14025-Prov), and of U.S. Provisional Patent Application No. 62,026,197, filed on July 18, 2014, entitled, "Methods and Compositions to Modify GSK-3 Activity" (Docket OHU 2035 MA/14006-Prov), and of U.S. Provisional Patent Application No. 62/026,234, filed July 18, 2014, entitled, "Imidazole and Thiazole Compositions for Modifying Biological Signaling" (Docket OHU 2036 MA/14001-Prov), the contents of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

[0002] The present disclosure relates generally to modulation of glycogen synthase kinase-3 [*i.e.*, GSK-3(α and/or β)] activity, modulation of GSK-3 signaling, and treatment of GSK-3 mediated disorders. More particularly, the present disclosure relates to one or more methods for modulating GSK-3 activity, modulating GSK-3 signaling, and treating GSK-3 mediated disorders using novel imidazole and/or thiazole compounds.

BACKGROUND

[0003] The protein kinases, of which there are over 500 in the human genome, are germane to cellular signal transduction and consequently to a plethora of cellular processes. The kinases bind to protein substrates and high energy donors (*e.g.* ATP) and transfer a phosphate group to the substrate. The aberrant activity of one particular kinase, glycogen synthase kinase-3 [*i.e.*, GSK-3(α and/or β)] has been implicated in a host of pathologies including malaria, cancer, insulin resistance, type 2 diabetes mellitus, muscle wasting (*i.e.*, muscle atrophy), neurodegenerative diseases, cardiovascular diseases, myocardial diseases, pathological inflammation, renal diseases, HIV-related neurological disorders, sepsis, toxic shock, psychiatric diseases, and central nervous system (*i.e.*, CNS) diseases.

[0004] GSK-3 is expressed as two isozymes, GSK-3 α and GSK-3 β . Though it is clear that the roles of these isozymes in pathology and physiology are not identical, the understanding of the differences in their function is in the early stages and the importance of developing α -specific

or β -specific inhibitors is unclear. To date, most inhibitors do not discriminate between these two isoforms.

[0005] The universe of inhibitors may be divided into three different types: (1) cations; (2) ATP-competitors; and (3) non-ATP competitors. Lithium, a cation widely used to treat bipolar and other severe mental disorders, is a relatively weak GSK-3 inhibitor. The reported mechanism is via competition with Mg^{2+} ions and enhancing serine phosphorylation. Other metals have also been shown to be inhibitors of GSK-3 including bivalent zinc ions.

[0006] Numerous ATP-competitors have been identified. These were obtained through modification of compounds that exist naturally (*e.g.*, indirubins) or through organic synthesis (*e.g.*, AR-R014418 and AZD-1080). Many of these agents are quite potent, having IC_{50} values in the nanomolar range. All of these compounds demonstrated biological activity and one, AZD-1080, did enter clinical trials but was withdrawn. The fact that all protein kinases have a binding pocket for a high energy donor that is typically ATP, raises the possibility that ATP-competitive inhibitors may have limited specificity. Some of the GSK-3 ATP-competitive inhibitors did show specificity against a small panel of kinases. It is possible that there are features of the ATP-binding pocket that are unique to GSK-3 and that can be exploited to generate inhibitors that are highly specific for GSK-3. Nevertheless, the potential lack of specificity of ATP-competitive inhibitors has led to an effort to identify non-ATP competitive inhibitors.

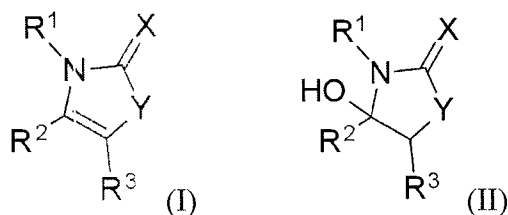
[0007] Although fewer non-ATP competitive GSK-3 inhibitors have been identified, several have been developed including those obtained from natural sources (*e.g.*, manzamines) or organic synthesis. In addition, a peptide (*e.g.*, L803-mts) has been developed that is a non-ATP competitive inhibitor. In general, these inhibitors tend to be less potent than the ATP-competitive inhibitors having IC_{50} values in the low micromolar range, compared to the nanomolar range often seen for ATP-competitive inhibitors. One set of inhibitors, generated through organic synthesis, are the Thiadiazolidindiones (*i.e.*, TDZD). The lead compound in this group, tideglusib (*i.e.*, NP-12) progressed favorably through clinical trials and entered two phase II clinical studies. One study, the TAUROS study for the treatment of progressive supranuclear palsy, did not meet its primary endpoint. Likewise, in the Phase IIb clinical trial for Alzheimer's disease, the primary endpoint was not achieved. In the former study, a positive clinical effect was observed in an analysis of a sub-set of patients in the group.

Specifically, those treated with tideglusib had reduced progression of global cerebral atrophy compared to placebo.

[0008] In view of the above background, there is an ongoing need for modulators, such as, *e.g.*, inhibitors, of GSK-3 activity and methods for modulating, such as, *e.g.*, inhibiting, GSK-3 activity, modulating GSK-3 signaling, and treating GSK-3 mediated disorders.

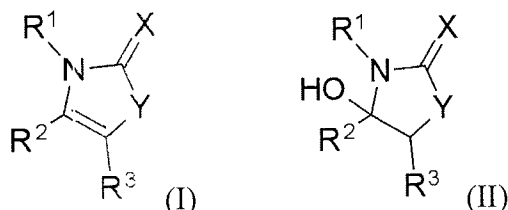
SUMMARY

[0009] The present disclosure is based on the discovery that imidazole and/or thiazole compounds can be used to modulate GSK-3 activity, to modulate GSK-3 signaling, and/or to treat GSK-3 mediated disorders. Accordingly, provided herein is an entirely new paradigm for disease intervention. In some embodiments, methods for modulating glycogen synthase kinase-3 (*i.e.*, GSK-3) activity in a cell expressing GSK-3 are provided. Such methods include contacting the cell with a therapeutically effective amount of at least one compound of General Formula (I) or (II):



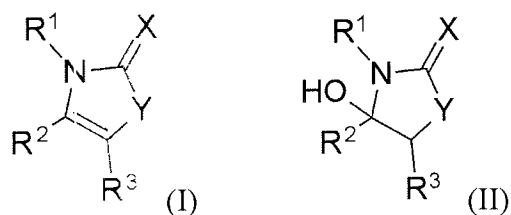
or a pharmaceutically-acceptable salt or solvate thereof, in which: R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH ; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0010] In embodiments, also provided are methods for modulating GSK-3 signaling. Such methods include contacting a cell expressing GSK-3 with a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which: R¹ is chosen from C₁ to C₁₀ aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R² is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R³ is chosen from -H, C₁ to C₁₀ aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O; and Y is S or NH; with the proviso that when R² is phenyl and R³ is -H, at least one of the following is true: (a) R¹ is a C₁ to C₁₀ aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R¹ is hexyl; (c) R¹ is Ph(CH₂)_n-, where n is 2 or 3; or (d) R¹ is a C₁ to C₁₀ heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0011] In other embodiments, also provided are methods for treating GSK-3-mediated disorders in a subject in need thereof. Such methods include administering to the subject a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which: R¹ is chosen from C₁ to C₁₀ aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination

thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH ; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0012] It is to be understood that both the foregoing general description and the following detailed description describe various embodiments and are intended to provide an overview or framework for understanding the nature and character of the claimed subject matter. The accompanying drawings are included to provide a further understanding of the various embodiments, and are incorporated into and constitute a part of this specification. The drawings illustrate the various embodiments described herein, and together with the description serve to explain the principles and operations of the claimed subject matter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A is a graph of COB-152 (*i.e.*, I-152) concentration (nM) with respect to percent inhibition of GSK-3 α activity;

[0014] FIG. 1B is a graph of COB-152 (*i.e.*, I-152) concentration (nM) with respect to percent inhibition of GSK-3 β activity;

[0015] FIG. 2A is a graph of COB-187 (*i.e.*, I-187) concentration (nM) with respect to percent inhibition of GSK-3 α activity;

[0016] FIG. 2B is a graph of COB-187 (*i.e.*, I-187) concentration (nM) with respect to percent inhibition of GSK-3 β activity;

[0017] FIG. 3 is a graph of cyclin-dependent kinases CDK1, CDK2, CDK/p25, CDK5/p35, CDK7, CDK8, CDK9 Cyclin K, CDK9 Cyclin T1, GSK-3 α (*i.e.*, GSK3 alpha) and GSK-3 β

(GSK3 beta) activity with respect to percent inhibition by COB-152 (*i.e.*, I-152) and/or COB-187 (*i.e.*, I-187);

[0018] FIG. 4A is a western blot of β -catenin, GSK-3 α , GSK-3 β , and β -actin (serving as a control) expression in RAW 264.7 murine macrophages treated with DMSO (0.1% v/v) or COB-152 (0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) for 5 hours;

[0019] FIG. 4B is a western blot of β -catenin, GSK-3 α , GSK-3 β , and β -actin (serving as a control) expression in RAW 264.7 murine macrophages treated with DMSO (0.1% v/v) or COB-187 (0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) for 5 hours;

[0020] FIG. 5A is a western blot of β -catenin, GSK-3 α , GSK-3 β , and β -actin (serving as a control) expression in PMA differentiated THP-1 cells treated with DMSO (0.1% v/v) or COB-152 (0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) for 5 hours;

[0021] FIG. 5B is a western blot of β -catenin, GSK-3 α , GSK-3 β , and β -actin (serving as a control) expression in PMA differentiated THP-1 cells treated with DMSO (0.1% v/v) or COB-187 (0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) for 5 hours;

[0022] FIG. 6A is a graph of untreated RAW 264.7 murine macrophages, RAW 264.7 murine macrophages treated with DMSO (0.1% v/v), and RAW 264.7 murine macrophages treated with COB-152 (4 μ M, 20 μ M, or 40 μ M) for 5 hours with respect to fold change in β -catenin mRNA expression;

[0023] FIG. 6B is a graph of untreated RAW 264.7 murine macrophages, RAW 264.7 murine macrophages treated with DMSO (0.1% v/v), and RAW 264.7 murine macrophages treated with COB-187 (4 μ M, 20 μ M, or 40 μ M) for 5 hours with respect to fold change in β -catenin mRNA expression;

[0024] FIG. 7 is a graph of untreated RAW 264.7 murine macrophages, LPS-induced RAW 264.7 murine macrophages, LPS-induced RAW 264.7 murine macrophages treated with DMSO (0.1% v/v), and LPS-induced RAW 264.7 murine macrophages treated with COB-152 (0.1 μ M, 1 μ M, or 10 μ M) for 4 hours with respect to fold change in IL-6 mRNA expression;

[0025] FIG. 8A is a graph of untreated human macrophages (*i.e.*, Untrx) and human macrophages treated with A β (1-42) peptides (*i.e.*, Abeta, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) for 5 and 24 hours with respect to fold change in IL-6 mRNA expression;

[0026] FIG. 8B is a graph of untreated human macrophages (*i.e.*, Untrx) and human macrophages treated with A β (1-42) peptides (*i.e.*, Abeta, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) for 5 and 24 hours with respect to fold change in TNF- α mRNA expression;

[0027] FIG. 8C is a graph of untreated human macrophages (*i.e.*, Untrx) and human macrophages treated with A β (1-42) peptides (*i.e.*, Abeta, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) for 5 and 24 hours with respect to fold change in IL-1 α mRNA expression;

[0028] FIG. 8D is a graph of untreated human macrophages (*i.e.*, Untrx) and human macrophages treated with A β (1-42) peptides (*i.e.*, Abeta, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) for 5 and 24 hours with respect to fold change in IL-1 β mRNA expression;

[0029] FIG. 9A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in IL-6 mRNA expression;

[0030] FIG. 9B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in IL-6 protein expression (pg/mL);

[0031] FIG. 9C is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in IL-6 mRNA expression;

[0032] FIG. 9D is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in IL-6 protein expression (pg/mL);

[0033] FIG. 10A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated

with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in TNF- α mRNA expression;

[0034] FIG. 10B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in TNF- α protein expression (pg/mL);

[0035] FIG. 10C is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in TNF- α mRNA expression;

[0036] FIG. 10D is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in TNF- α protein expression (pg/mL);

[0037] FIG. 11A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in IL-1 β mRNA expression;

[0038] FIG. 11B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, or 25 μ M) stimulated with A β (1-42) peptides (10 μ M) for 5 hours with respect to fold change in IL-1 β protein expression (pg/mL);

[0039] FIG. 11C is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with A β (1-42) peptides (10 μ M), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10

μM , or 25 μM) stimulated with $\text{A}\beta(1-42)$ peptides (10 μM) for 5 hours with respect to fold change in IL-1 β mRNA expression;

[0040] FIG. 11D is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with $\text{A}\beta(1-42)$ peptides (10 μM), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μM , 0.05 μM , 0.1 μM , 0.5 μM , 1 μM , 5 μM , 10 μM , or 25 μM) stimulated with $\text{A}\beta(1-42)$ peptides (10 μM) for 5 hours with respect to fold change in IL-1 β protein expression (pg/mL);

[0041] FIG. 12A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with $\text{A}\beta(1-42)$ peptides (10 μM), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μM , 0.05 μM , 0.1 μM , 0.5 μM , 1 μM , 5 μM , 10 μM , or 25 μM) stimulated with $\text{A}\beta(1-42)$ peptides (10 μM) for 5 hours with respect to fold change in IL-1 α mRNA expression;

[0042] FIG. 12B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with $\text{A}\beta(1-42)$ peptides (10 μM), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μM , 0.05 μM , 0.1 μM , 0.5 μM , 1 μM , 5 μM , 10 μM , or 25 μM) stimulated with $\text{A}\beta(1-42)$ peptides (10 μM) for 5 hours with respect to fold change in IL-1 α mRNA expression;

[0043] FIG. 13A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with $\text{A}\beta(1-42)$ peptides (10 μM), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μM , 0.05 μM , 0.1 μM , 0.5 μM , 1 μM , 5 μM , 10 μM , or 25 μM) stimulated with $\text{A}\beta(1-42)$ peptides (10 μM) for 5 hours with respect to fold change in IFN- β mRNA expression;

[0044] FIG. 13B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with $\text{A}\beta(1-42)$ peptides (10 μM), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μM , 0.05 μM , 0.1 μM , 0.5 μM , 1 μM , 5 μM , 10 μM , or 25 μM) stimulated with $\text{A}\beta(1-42)$ peptides (10 μM) for 5 hours with respect to fold change in IFN- β mRNA expression;

[0045] FIG. 14A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μM , 0.05 μM , 0.1 μM , 0.5 μM , 1 μM , 5 μM , 10 μM , 25 μM , or

50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-6 mRNA expression;

[0046] FIG. 14B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-6 protein expression (pg/mL);

[0047] FIG. 14C is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-6 mRNA expression;

[0048] FIG. 14D is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-6 protein expression (pg/mL);

[0049] FIG. 15A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in TNF- α mRNA expression;

[0050] FIG. 15B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in TNF- α protein expression (pg/mL);

[0051] FIG. 15C is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or

50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in TNF- α mRNA expression;

[0052] FIG. 15D is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in TNF- α protein expression (pg/mL);

[0053] FIG. 16A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-1 β mRNA expression;

[0054] FIG. 16B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-1 β protein expression (pg/mL);

[0055] FIG. 16C is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-1 β mRNA expression;

[0056] FIG. 16D is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-1 β protein expression (pg/mL);

[0057] FIG. 17A is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-152 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or

50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-1 α mRNA expression;

[0058] FIG. 17B is a graph of untreated human macrophages (*i.e.*, Untrx), human macrophages stimulated with LPS (10 ng/mL), and human macrophages treated with DMSO (0.1% v/v) or COB-187 (0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M, 1 μ M, 5 μ M, 10 μ M, 25 μ M, or 50 μ M) stimulated with LPS (10 ng/mL) for 5 hours with respect to fold change in IL-1 α mRNA expression; and

[0059] FIG. 18 is a graph of untreated murine macrophages, murine macrophages stimulated with LPS, and murine macrophages treated with DMSO, macrophages treated with COB-152 (0.1 μ M, 1 μ M, or 10 μ M) with respect to iNOS fold expression.

DETAILED DESCRIPTION

[0060] While the following terms are believed to be well understood by one of ordinary skill in the art, definitions are set forth to facilitate explanation of the presently-disclosed subject matter.

[0061] In embodiments, the terms “modulate”, “modulation”, and “modulating” refer to reducing, terminating, and/or enhancing activity of an enzyme, such as, *e.g.*, GSK-3 activity. In other embodiments, the terms “modulate”, “modulation”, and “modulating” refer to preventing, reducing, enhancing and/or terminating the expression and/or function of messenger molecules in a signaling pathway. In embodiments related to GSK-3, imidazole and/or thiazole compounds may be effective to modulate signaling of GSK-3 by preventing, reducing, enhancing, and/or terminating expression and/or function of messenger molecules upstream and/or downstream of GSK-3. For example, imidazole and/or thiazole compounds may be effective to modulate signaling of GSK-3 by enhancing expression of β -catenin, inhibiting function of lipopolysaccharide, and/or suppressing expression of i-Nitrous Oxide Synthase.

[0062] In embodiments, the terms “inhibit”, “inhibition”, and “inhibiting” refer to reducing and/or terminating activity of an enzyme, such as, *e.g.*, GSK-3 activity. For example, in some embodiments, imidazole and/or thiazole compounds recognize, bind to, and/or otherwise combine with GSK-3 in a way that influences the binding of GSK-3 substrates thereto and/or in a way that influences the turnover number of GSK-3. In other embodiments, the term

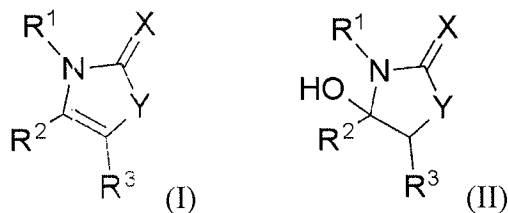
“inhibit”, “inhibition”, and “inhibiting” refer to preventing and/or terminating the expression and/or function of signaling molecules in a signaling pathway.

[0063] The term “GSK-3” refers to the enzyme glycogen synthase kinase 3 and homologs thereof.

[0064] The term “activity” refers to a measure of active enzyme, such as, *e.g.*, GSK-3, present. More specifically, in embodiments, enzyme activity refers to the ability of an enzyme to convert a substrate into a product. Quantitatively, enzyme activity refers to moles of substrate converted to product per unit time.

[0065] The term “therapeutically effective amount” as used herein, refers to an amount necessary or sufficient to realize a desired biologic effect. The therapeutically effective amount may vary depending on a variety of factors known to those of ordinary skill in the art, including but not limited to, the particular composition being administered, the activity of the composition being administered, the size of the subject, the sex of the subject, the age of the subject, the general health of the subject, the timing and route of administration, the rate of excretion, the administration of additional medications, and/or the severity of the disease or disorder being prevented and/or treated. In some embodiments, the term therapeutically effective amount refers to the amount of imidazole and/or thiazole compounds and, more specifically, imidazole 2-thiones, imidazole 2-ones, thiazole 2-thiones, and/or thiazole 2-ones, necessary or sufficient to inhibit GSK-3 activity, to modulate GSK-3 signaling, and/or to treat GSK-3-mediated disorders and/or diseases.

[0066] The terms “imidazole compounds” and/or “thiazole compounds”, as used herein, refer to and/or are limited to the compositions having the following general structural formulae:

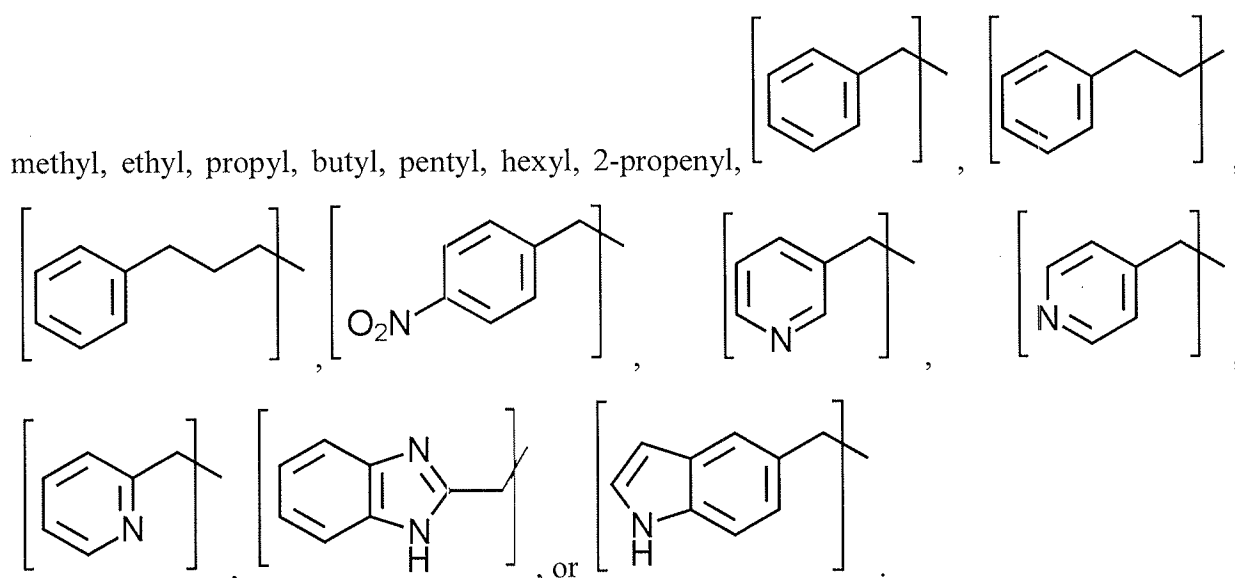


or pharmaceutically-acceptable salts or solvates thereof.

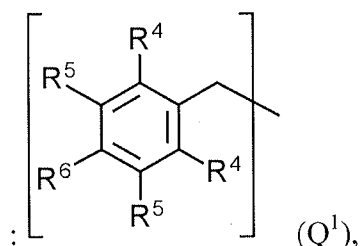
[0067] In the imidazole compounds and thiazole compounds having general structural formulae (I) and (II): R¹ is chosen from C₁ to C₁₀ aliphatic or heteroaliphatic groups, the C₁ to C₁₀ aliphatic or heteroaliphatic groups being substituted with one or more heteroaryl groups, substituted heteroaryl groups, or combination thereof; R² is chosen from aromatic moieties,

substituted aromatic moieties, heteroaromatic moieties, substituted heteroaromatic moieties, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH , with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; or (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0068] In the compounds of General Formula (I) and General Formula (II), group R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof. In illustrative non-limiting embodiments, group R^1 is chosen from

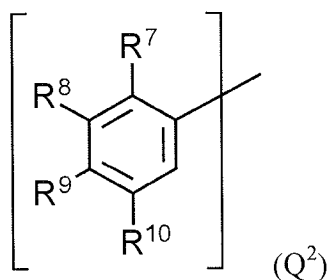


[0069] In other illustrative embodiments, group R^1 may have be a group Q^1 :



in which groups R^4 , R^5 , and R^6 are independently chosen from $-H$, halo (such as $-F$, $-Cl$, or $-Br$), $-NO_2$, $-CN$, or alkylesters such as $-OCH_3$. In other illustrative embodiments, group R^1 may be a group Q^1 , in which groups R^4 and R^5 all are H and group R^6 is chosen from alkylesters, Cl , $-NO_2$, or $-CN$.

[0070] In the compounds of General Formula (I) and General Formula (II), group R^2 is chosen from unsubstituted aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin. In some embodiments, group R^2 may be an unsubstituted phenyl group, a 2-monosubstituted phenyl group, a 3-monosubstituted phenyl group, a 4-monosubstituted phenyl group, a 2,3-disubstituted phenyl group, a 2,4-disubstituted phenyl group, a 2,5-disubstituted phenyl group, a 3,4-disubstituted phenyl group, or a 3,5-disubstituted phenyl group. In such embodiments, group R^2 may be a group Q^2 :



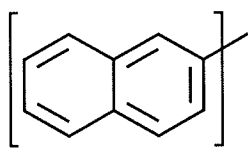
[0071] In embodiments in which group R^2 is a monosubstituted phenyl group Q^2 , in group Q^2 exactly three of any of R^7 , R^8 , R^9 , and R^{10} are hydrogen, and the one of R^7 , R^8 , R^9 , and R^{10} that is not hydrogen may be chosen from methoxy, ethoxy, hydroxy, trifluoromethoxy, methyl, trifluoromethyl, *N*-methylamino, (*N,N*)-dimethylamino, cyano, halo (for example, chloro, fluoro, or bromo), or nitro, for example.

[0072] In embodiments in which group R^2 is a disubstituted phenyl group Q^2 , in group Q^2 exactly two of any of R^7 , R^8 , R^9 , and R^{10} are hydrogen, and the two groups of R^7 , R^8 , R^9 , and R^{10} that are not hydrogen may be independently chosen from methoxy, ethoxy, hydroxy, trifluoromethoxy, dimethylamino, cyano, chloro, fluoro, or nitro, for example.

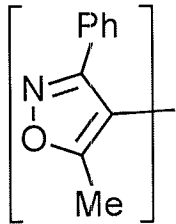
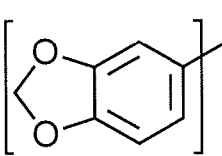
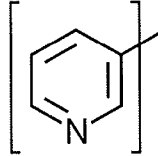
[0073] In some embodiments in which group R^2 is a disubstituted phenyl group Q^2 , group Q^2 may be any isomer of hydroxyphenyl, dihydroxyphenyl, methoxyphenyl, dimethoxyphenyl, halophenyl, dihalophenyl, chlorophenyl, dichlorophenyl, fluorophenyl, halohydroxyphenyl, halomethoxyphenyl, chlorohydroxylphenyl, chloromethoxyphenyl, fluorohydroxyphenyl, fluoromethoxyphenyl.

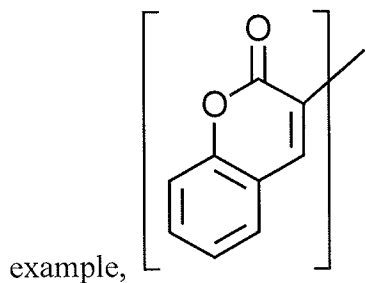
[0074] Illustrative, non-limiting examples of group R^2 as a monosubstituted phenyl group Q^2 or a disubstituted phenyl group Q^2 may include 2-methoxyphenyl; 3-methoxyphenyl; 3-chlorophenyl; 2,5-dimethoxyphenyl; 2,4-dimethoxyphenyl; 3,4-dimethoxyphenyl; 4-(dimethylamino)phenyl; 4-(trifluoromethoxy)phenyl; 4-cyanophenyl; 3-hydroxyphenyl; 2,4-hydroxyphenyl; 3,4-dichlorophenyl; 3-nitrophenyl; 2-hydroxy-5-chlorophenyl; 2-methylphenyl; 2,5-dimethylphenyl; 2-methoxy-5-fluorophenyl; and 2-chloro-5-(trifluoromethyl)phenyl.

[0075] In other embodiments, group R^2 may be an aryl group such as, for example,

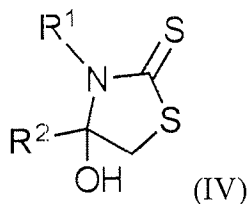
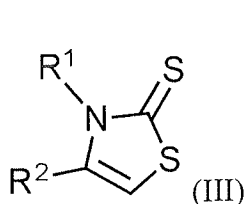


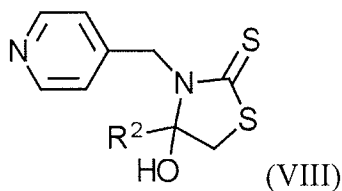
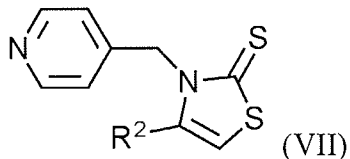
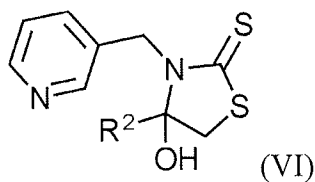
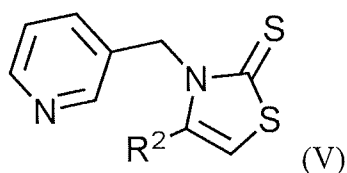
, or a substituted derivative thereof. In other embodiments, group R^2 may be an aryl group other than phenyl. In other embodiments, group R^2 may be a heteroaryl group

such as, for example, , , , or substituted derivatives of any of these. In other embodiments, group R^2 may be coumarin, such as, for



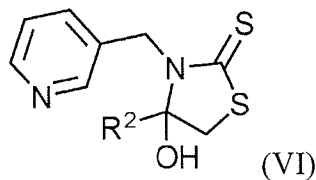
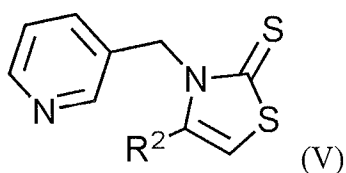
[0076] In some embodiments, preferred compounds of General Formula (I) and General Formula (II) may include compounds of formulas (III)–(VIII):





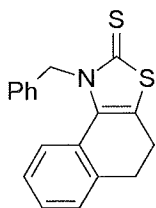
in which groups R^1 and R^2 are as described above and groups R^3 of formulas (I) and (II) are hydrogen.

[0077] In some embodiments, preferred compounds of General Formula (I) and General Formula (II) may include compounds of formulas (V) or (VI):



in which group R^2 is as described above.

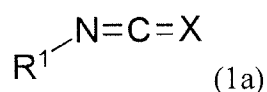
[0078] In the compounds of General Formula (I) and General Formula (II), group R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof. In non-limiting exemplary embodiments, R^3 may be methyl, ethyl, *n*-propyl, isopropyl, butyl, 3-butenyl, phenyl, or 2-phenylethyl. In some embodiments, R^3 is hydrogen. The aliphatic or heteroaliphatic groups of R^3 optionally may be bonded to group R^2 to form a ring. One illustrative example of an aliphatic group R^3 bonded to group R^2 to form a ring is the structure



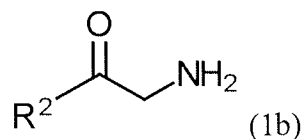
having General Formula (I), in which group R^1 attached to the nitrogen atom is phenylmethyl (benzyl), group R^2 is phenyl and group R^3 is an ethyl group bonded to the 2-position of the phenyl ring of R^2 to form a six-membered ring including all of group R^3 and part of group R^2 .

[0079] In the compounds of General Formula (I) and General Formula (II), X is S or O; and Y is S or NH. Thus, in some embodiments, group X is S and group Y is S. In other embodiments, group X is S and group Y is NH. In other embodiments, group X is O and group Y is S. In other embodiments, group X is O and group Y is NH.

[0080] The compounds of General Formula (I) and General Formula (II) may be prepared using any suitable synthetic scheme. In one exemplary synthetic scheme, the compounds having General Formula (I) in which X = O or S and Y = NH may be synthesized by adding an isothiocyanate or isocyanate of formula (1a):



(100 mol%, X = O or S) and Et₃N (50 mol.%) to an EtOH (0.01 M) solution of a hydrochloride of a methylamino ketone of formula (1b) (100 mol.%):

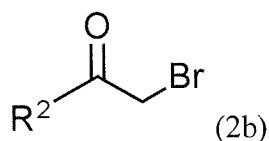


to form a reaction mixture. The reaction mixture may be heated at a suitable reaction temperature for a suitable time. If the heating is accomplished using microwave irradiation, the rate of elimination of a hydroxyl group from the product is increased, so as to substantially favor formation of compounds of General Formula (I) over those of General Formula (II). Conversely, application of heat without microwave irradiation favors compounds of General Formula (II) as products. The solvent may be removed, and the product may be isolated by flash chromatography, for example.

[0081] Compounds having General Formula (II) in which X = S and Y = S may be synthesized by adding carbon disulfide (CS₂; 150 mol.%) and K₂CO₃ (50 mol.%) to a solution of an amine (150 mol.%) of the formula (2a):



[0082] in H₂O:EtOH (0.2 M, 1:1) and then adding a 2-bromoketone derivative (100 mol%) of formula (2b):

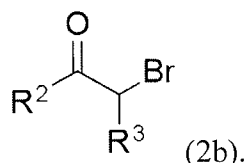


to form a reaction mixture. After stirring, a crude reaction mixture may be extracted with a solvent such as ethyl acetate, and the combined organic layers may be dried and filtered. The solvent may be evaporated by rotary evaporation. The product may be isolated using a solvent such as 10%-20% EtOAc in hexanes. In some cases, some products may precipitate during the reaction. In such cases the product may be isolated by filtration, washed thoroughly with solvent, then dried.

[0083] Compounds having General Formula (II), where $X = O$ and $Y = S$, may be synthesized by adding a solution of carbonyl sulfide (COS ; 150 mol.%) and K_2CO_3 (50 mol.%) to a solution of an amine (150 mol.%) of the formula (2a):



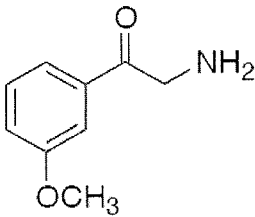
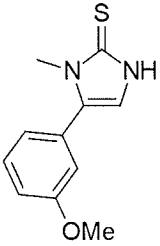
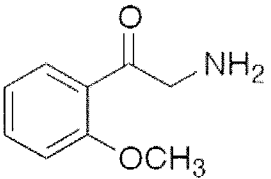
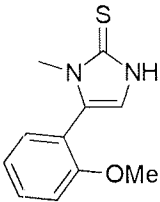
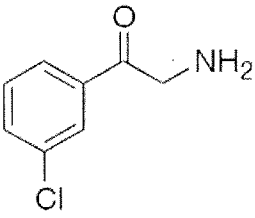
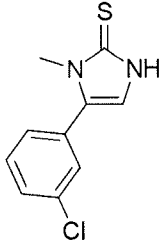
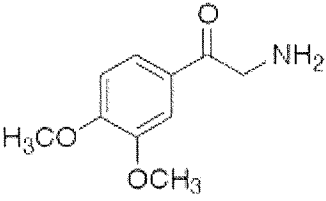
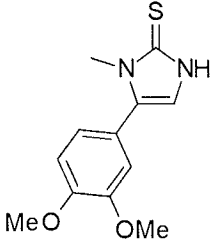
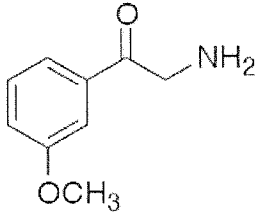
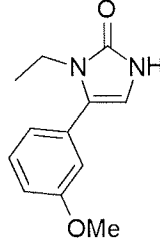
in $\text{H}_2\text{O}:\text{EtOH}$ (0.2 M, 1:1) and then adding a 2-bromoketone derivative (100 mol%) of formula (2b):

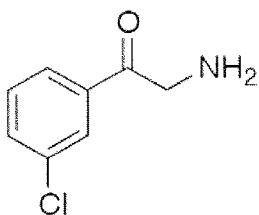
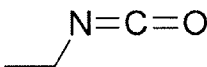
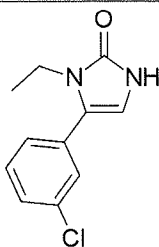
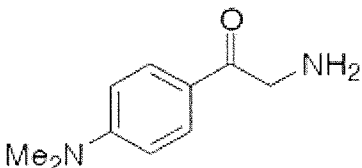
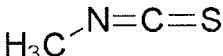
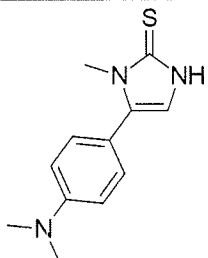
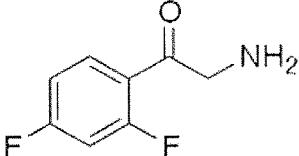
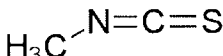
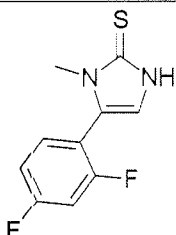
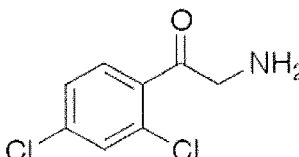
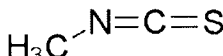
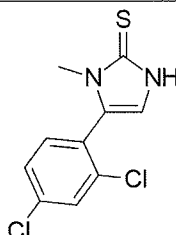
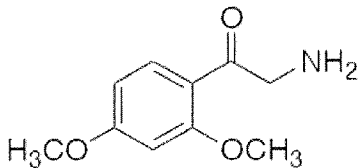
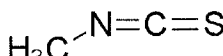
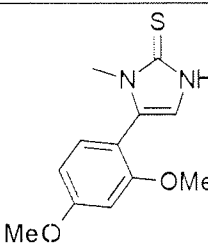
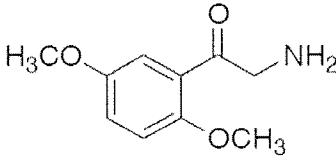
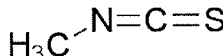
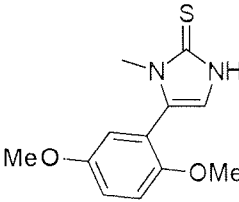


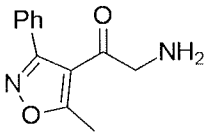
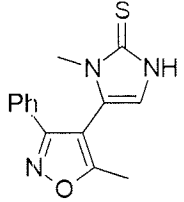
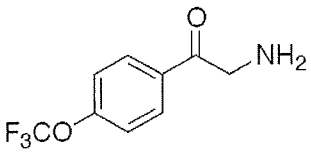
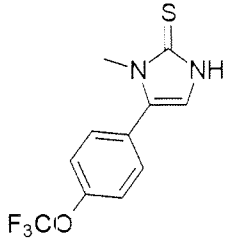
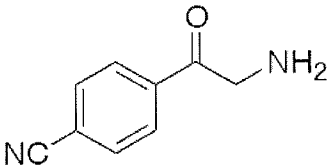
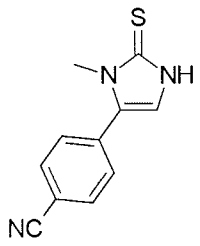
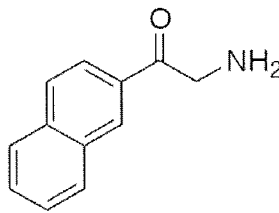
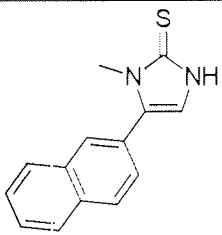
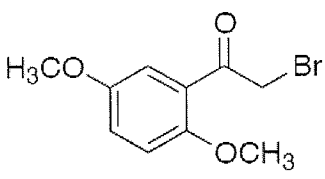
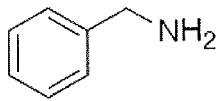
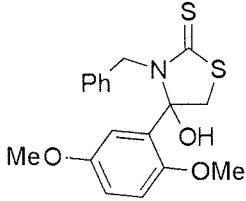
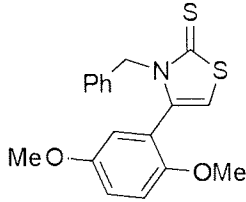
[0084] Compounds having General Formula (I), in which $X = O$ or S and $Y = S$, may be synthesized by dehydrating a compound having General Formula (II) prepared according by any suitable synthetic route, such as the route described above, for example, in which groups R^1 , R^2 , X , and Y of the compound having General Formula (II) are the same as those in the desired compound having General Formula (I).

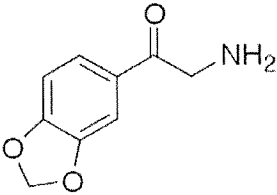
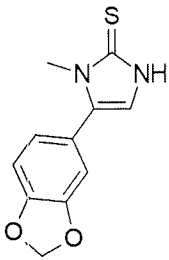
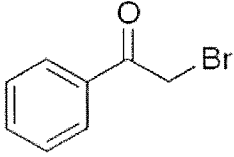
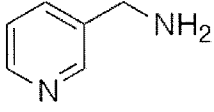
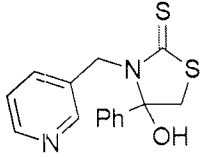
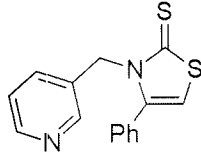
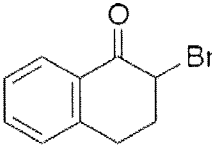
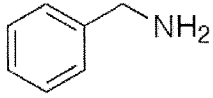
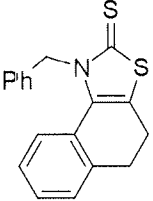
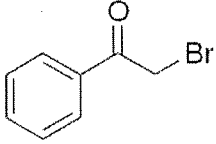
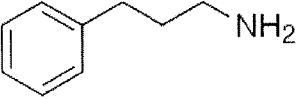
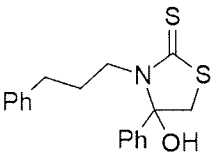
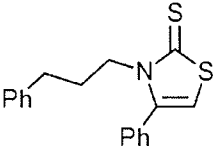
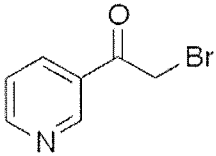
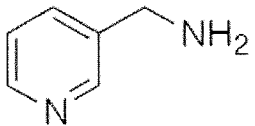
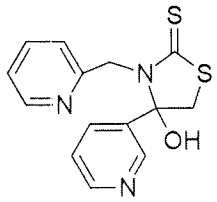
[0085] In TABLE 1 below, compounds having General Formula (I) or (II) according to various embodiments are provided, along with exemplary reactants for forming the compound having General Formula (I) or (II) according to the synthetic schemes described above and further described in the Examples section below:

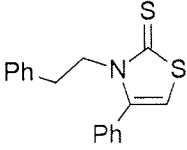
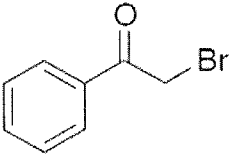
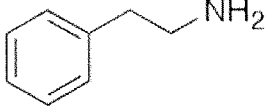
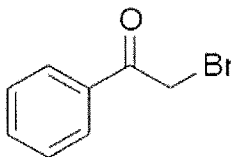
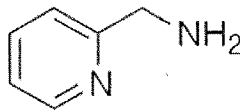
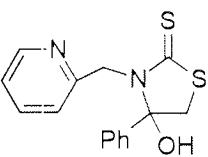
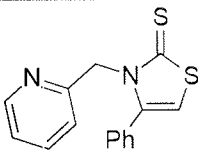
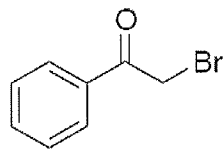
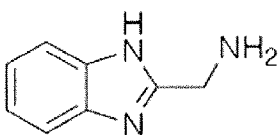
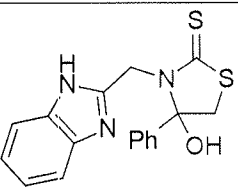
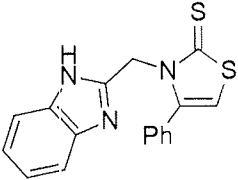
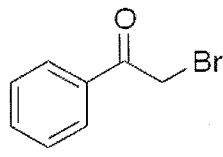
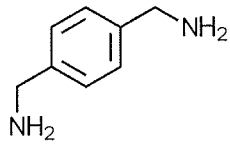
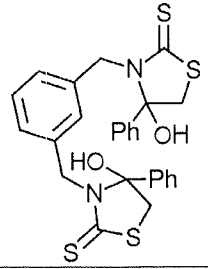
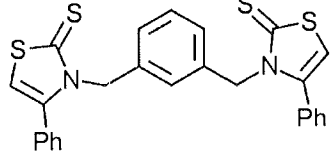
TABLE 1

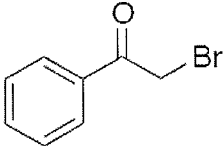
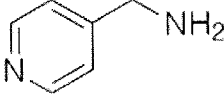
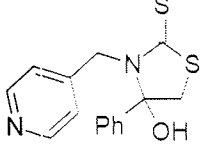
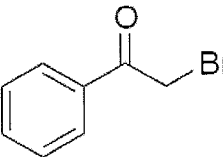
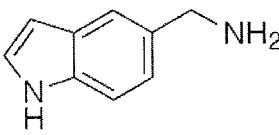
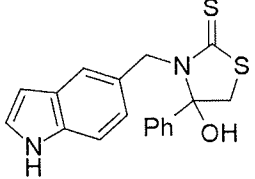
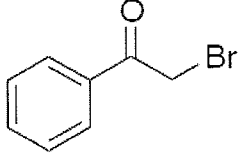
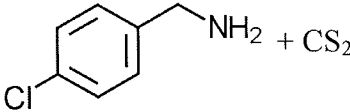
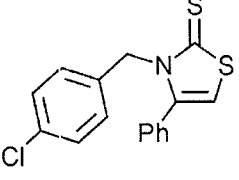
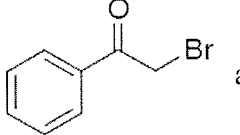
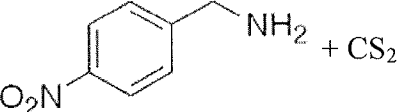
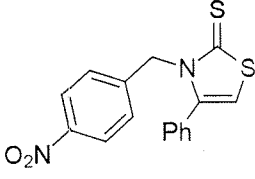
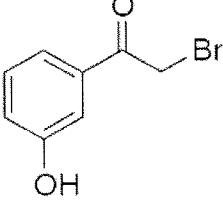
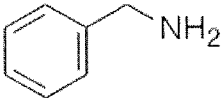
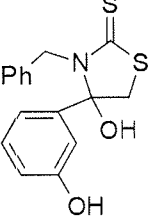
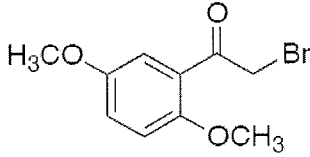
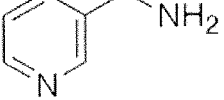
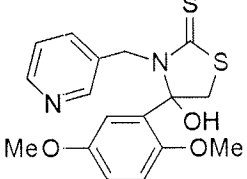
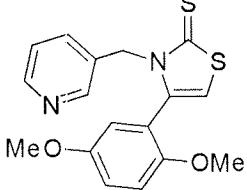
Reference	Reactant (1a) or (2a)	Reactant (1b) or (2b)	Compound of General Formula (I) or (II)
COB-117		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-118		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-119		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-123		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-124		$\text{CH}_3\text{CH}_2-\text{N}=\text{C}=\text{O}$	

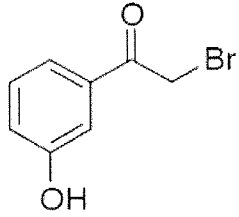
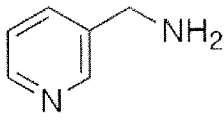
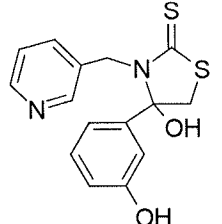
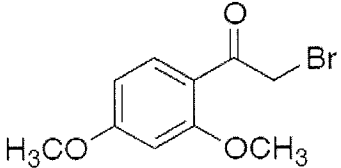
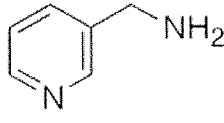
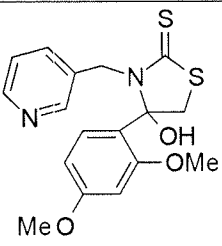
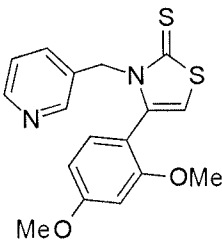
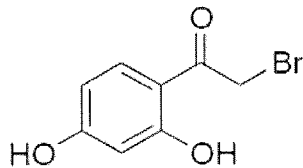
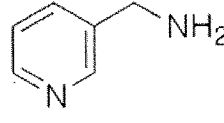
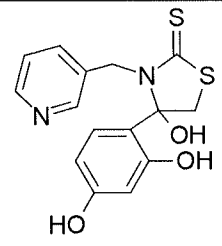
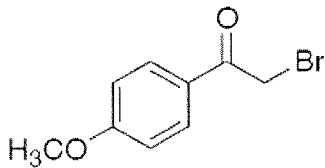
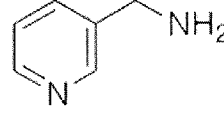
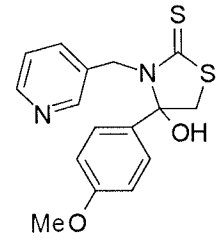
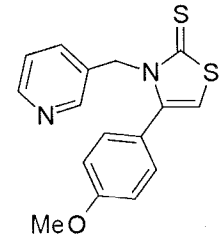
COB-125			
COB-126			
COB-128			
COB-129			
COB-130			
COB-132			

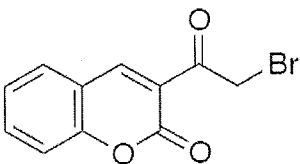
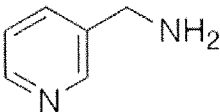
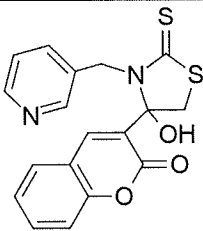
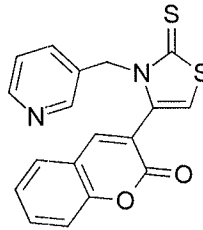
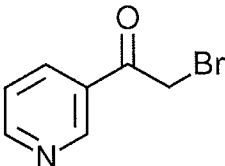
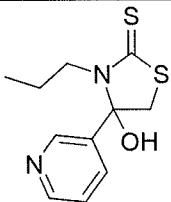
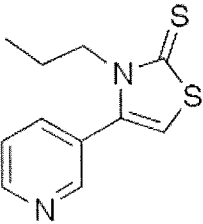
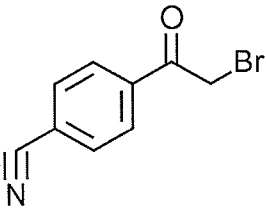
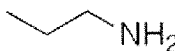
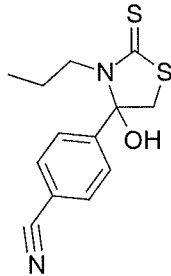
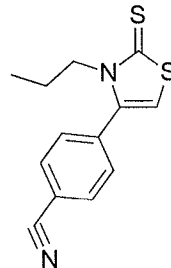
COB-133		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-134		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-138		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-139		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-143		 CS_2	
COB-144	Dehydration of COB-143		

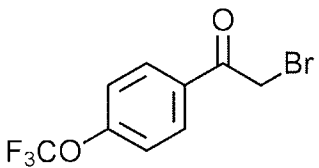
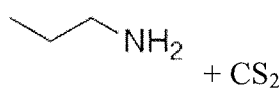
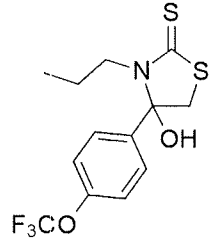
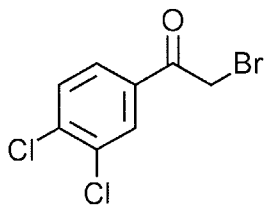
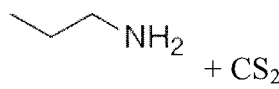
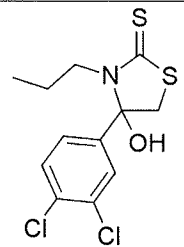
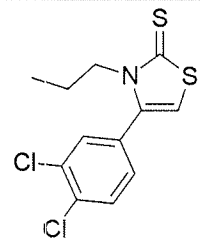
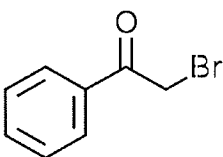
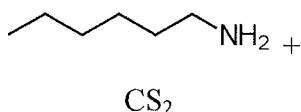
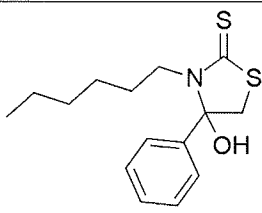
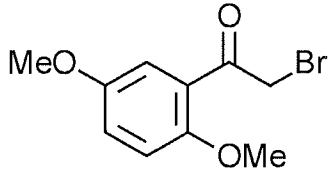
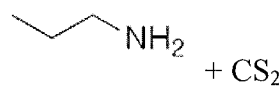
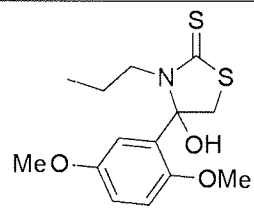
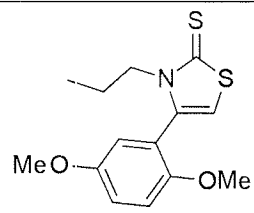
COB-146		$\text{H}_3\text{C}-\text{N}=\text{C}=\text{S}$	
COB-152		 + CS_2	
COB-153	Dehydration of COB-152		
COB-161			
COB-168		 + CS_2	
COB-178	Dehydration of COB-168		
COB-176		 + CS_2	

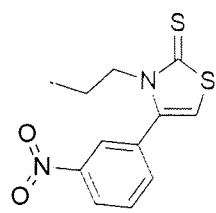
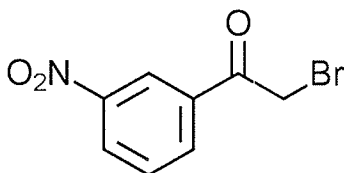
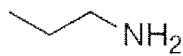
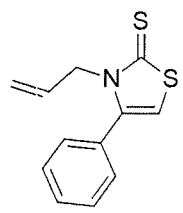
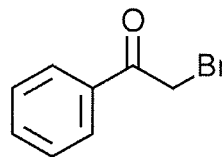
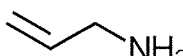
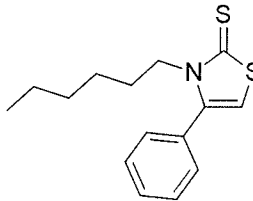
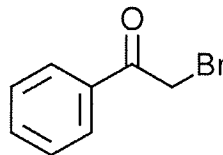
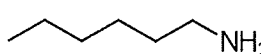
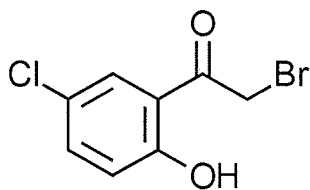
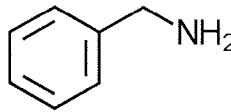
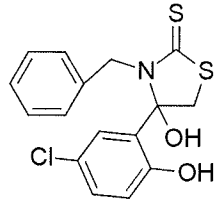
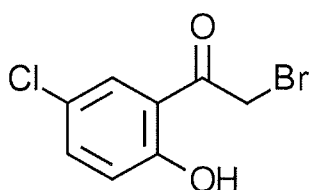
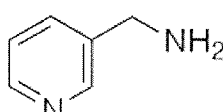
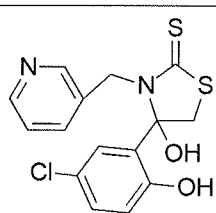
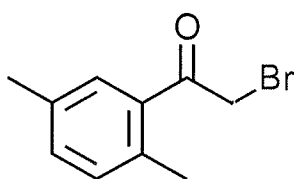
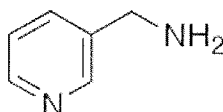
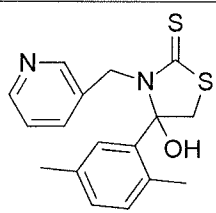
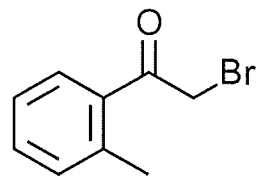
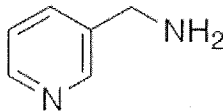
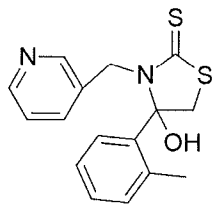
COB-177	Dehydration of reaction product of		
		and  + CS ₂	
COB-180		 + CS ₂	
COB-189	Dehydration of COB-180		
COB-183		 + CS ₂	
COB-192	Dehydration of COB-183		
COB-186	2 × 	 + CS ₂	
COB-193	Dehydration of COB-186		

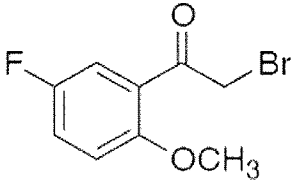
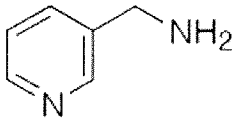
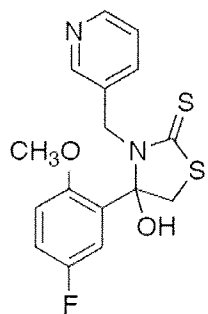
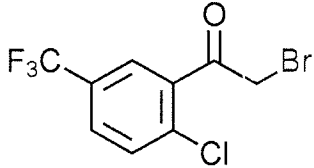
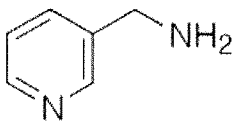
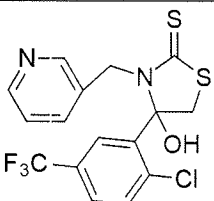
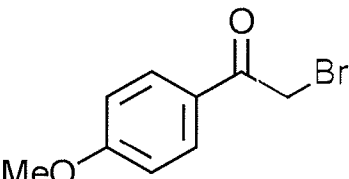
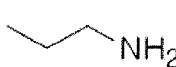
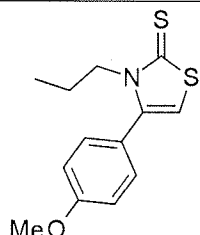
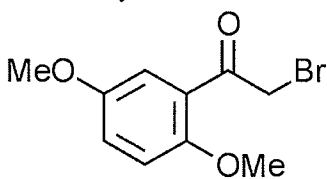
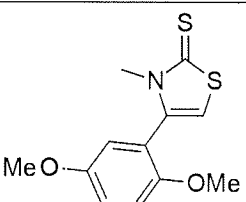
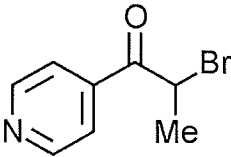
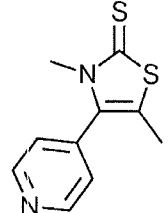
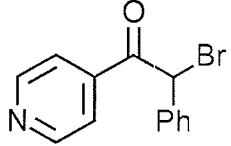
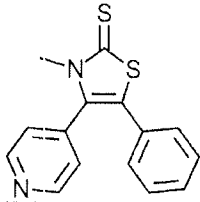
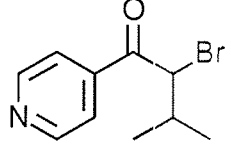
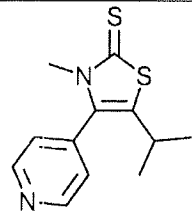
COB-187		 CS ₂ +	
COB-188		 + CS ₂	
COB-190	Dehydration of reaction product of  and  + CS ₂		
COB-191	Dehydration of reaction product of  and  + CS ₂		
COB-196		 CS ₂ +	
COB-197		 CS ₂ +	
COB-203	Dehydration of COB-197		

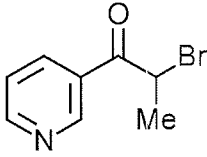
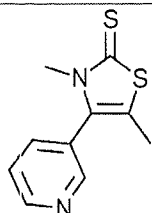
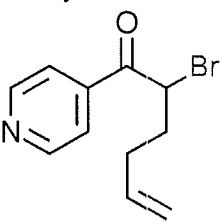
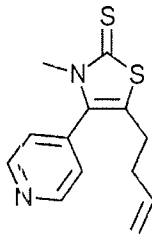
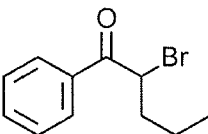
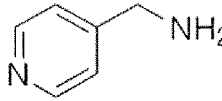
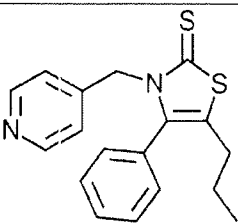
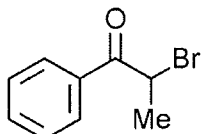
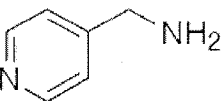
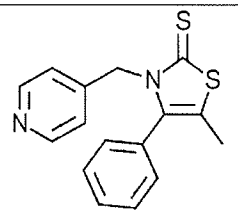
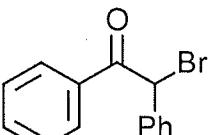
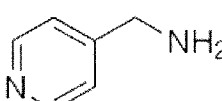
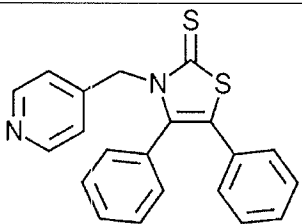
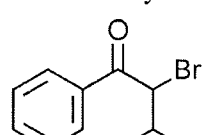
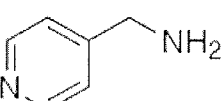
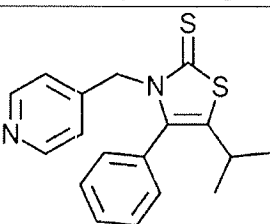
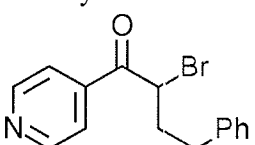
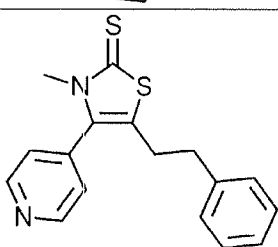
COB-198		 CS ₂ +	
COB-199		 CS ₂ +	
COB-204	Dehydration of COB-199		
COB-200		 CS ₂ +	
COB-201		 CS ₂ +	
COB-206	Dehydration of COB-201		

COB-202		 CS ₂ +	
COB-205	Dehydration of COB-202		
COB-207		 + CS ₂	
COB-214	Dehydration of COB-207		
COB-208		 + CS ₂	
COB-216	Dehydration of COB-208		

COB-209			
COB-210			
COB-219	Dehydration of COB-210		
COB-212			
COB-213			
COB-220	Dehydration of COB-213		

COB-215	Dehydration of reaction product of		
		and  + CS ₂	
COB-217	Dehydration of reaction product of		
		and  + CS ₂	
COB-218	Dehydration of reaction product of		
		and  + CS ₂	
COB-221		 + CS ₂	
COB-222		 + CS ₂	
COB-223		 + CS ₂	
COB-224		 + CS ₂	

COB-225		 + CS_2	
COB-226		 + CS_2	
DRB-3	Dehydration of reaction product of:  and  + CS_2		
GWB-93	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$		
Z-01	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$		
Z-02	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$		
Z-03	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$		

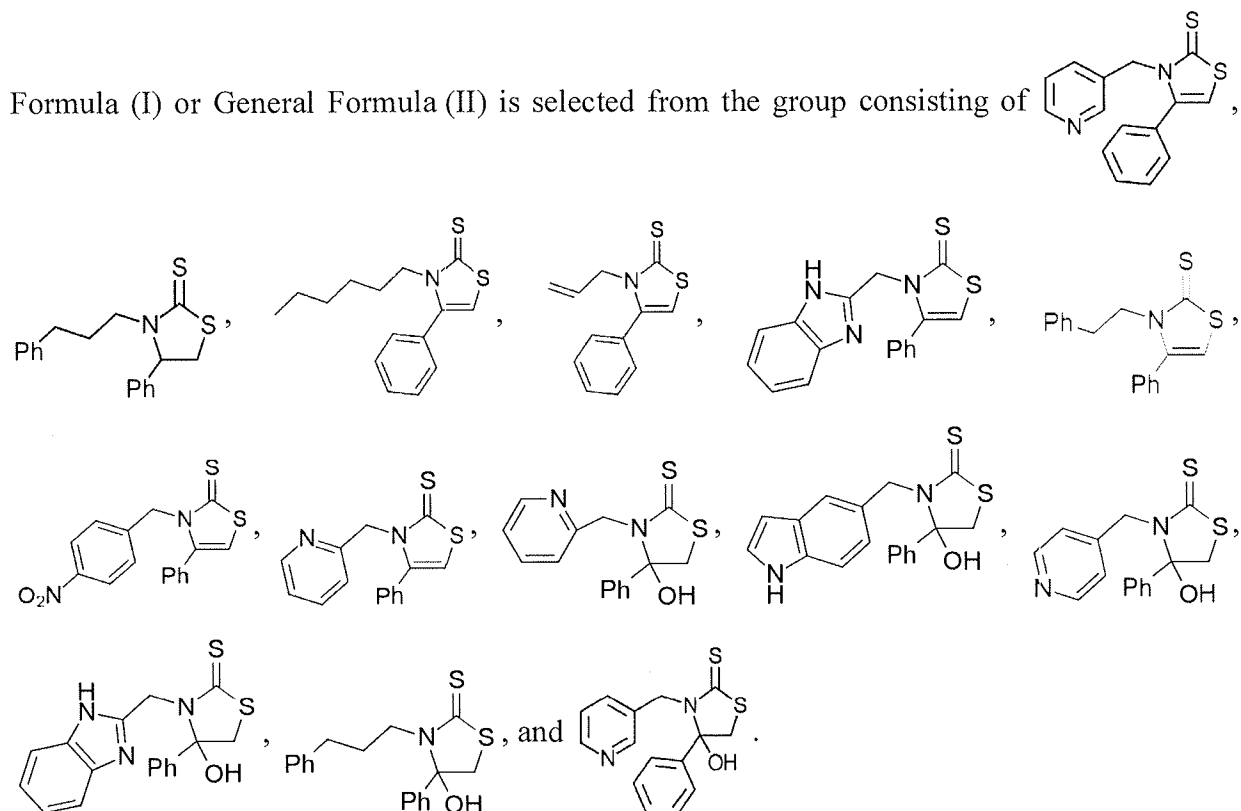
Z-04	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$	
Z-05	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$	
Z-06	Dehydration of reaction product of:  and  + CS_2	
Z-07	Dehydration of reaction product of:  and  + CS_2	
Z-08	Dehydration of reaction product of:  and  + CS_2	
Z-09	Dehydration of reaction product of:  and  + CS_2	
Z-10	Dehydration of reaction product of:  and $\text{CH}_3\text{NH}_2 + \text{CS}_2$	

[0086] The compounds of General Formula (I) and General Formula (II) may be generally described as a class of compounds composed of four genera: (1) imidazole 2-thiones (in which group X is S and group Y is NH); (2) imidazole 2-ones (in which group X is O and group Y is NH); (3) thiazole 2-thiones (in which group X is S and group Y is S); and (4) thiazole 2-ones (in which group X is O and group Y is S).

[0087] According to some embodiments, in the compounds of General Formula (I) and General Formula (II), when R^2 is phenyl and R^3 is hydrogen, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; or (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3 (i.e., group R^1 is 2-phenylethyl or 3-phenylpropyl); or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof. According to such embodiments, compounds of General Formula (I) and General Formula (II) do not include compounds in which group R^2 is phenyl and group R^1 is an unsubstituted aliphatic group other than hexyl.

[0088] In general, the provisos (a)–(d) define the scope of General Formula (I) and General Formula (II) when R^2 is phenyl and R^3 is hydrogen, based on the identity of R^1 . For example, considering all provisos together, when R^2 is phenyl and R^3 is hydrogen, C_1 to C_{10} aliphatic groups R^1 as defined under proviso (a) must be substituted with at least one substituted aryl group, at least one heteroaryl group, or at least one substituted heteroaryl group. Proviso (b) adds $R^1 = \text{hexyl}$ to the definition of C_1 to C_{10} aliphatic groups from proviso (a), and proviso (c) adds 2-phenylethyl and 3-phenylpropyl to the definition of C_1 to C_{10} aliphatic groups from proviso (a). That is, when R^2 is phenyl and R^3 is hydrogen, C_1 to C_{10} aliphatic groups R^1 do not include unsubstituted aliphatic groups such as methyl, ethyl, isopropyl, or cyclohexyl but do include hexyl groups. Likewise, when R^2 is phenyl and R^3 is hydrogen, C_1 to C_{10} aliphatic groups R^1 do not include aliphatic groups substituted with aryl groups that themselves are not substituted (such as phenyl), with the exception from proviso (c) that R^1 may be 2-phenylethyl or 3-phenylpropyl. In view of proviso (d), however, even when R^2 is phenyl and R^3 is hydrogen, C_1 to C_{10} heteroaliphatic groups R^1 may be unsubstituted or substituted. When the C_1 to C_{10} heteroaliphatic groups R^1 are substituted, they may be substituted with one or more aryl groups (even unsubstituted aryl groups), substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combinations thereof.

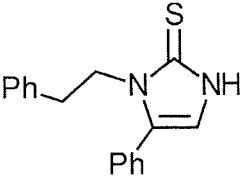
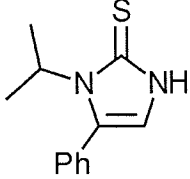
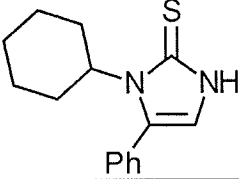
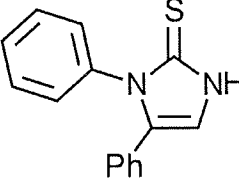
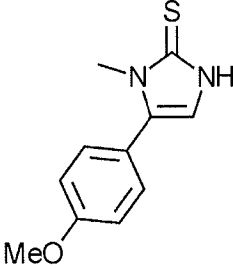
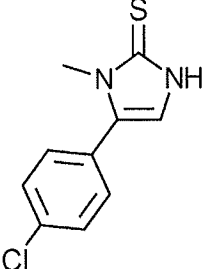
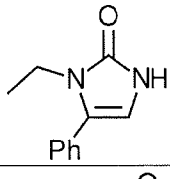
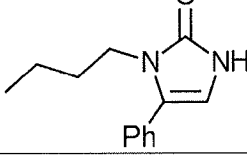
[0089] According to some embodiments, in the compounds of General Formula (I) and General Formula (II), when R^2 is phenyl and R^3 is hydrogen, the compound having General

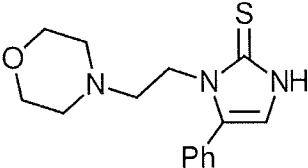
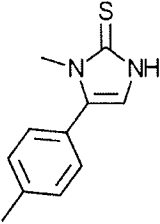
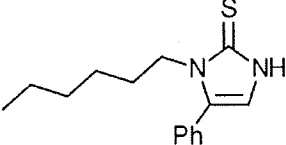
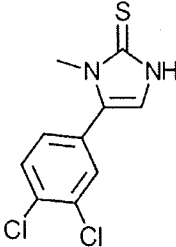
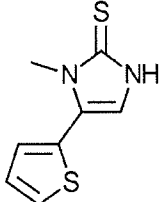
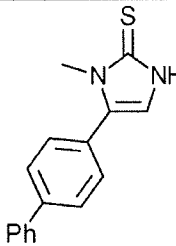
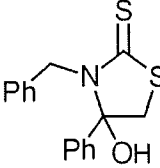
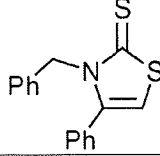
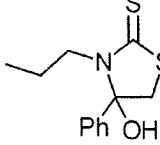


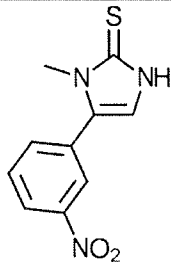
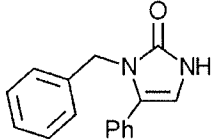
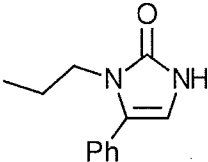
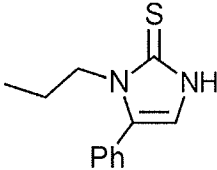
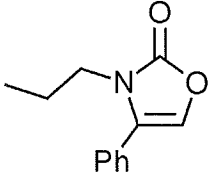
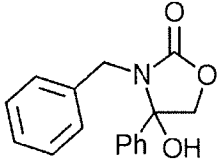
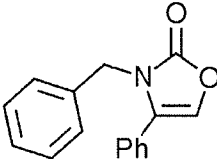
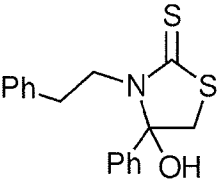
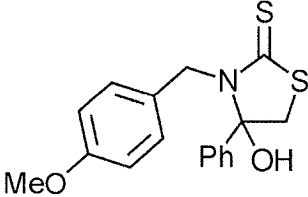
[0090] In some embodiments, the compounds of General Formula (I) or General Formula (II) do not include one or more of the compounds listed in **TABLE 2**, or may not include any of the compounds listed in **TABLE 2**.

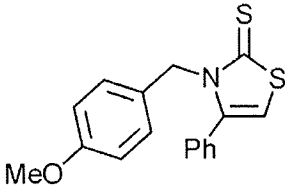
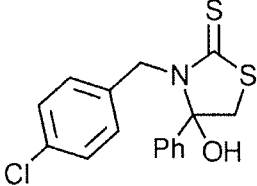
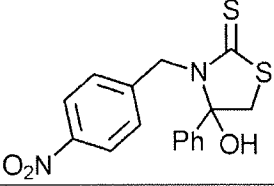
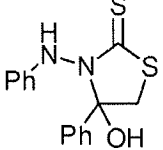
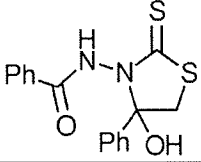
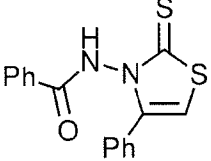
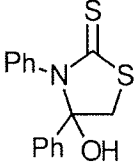
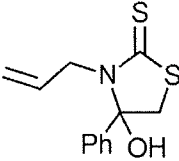
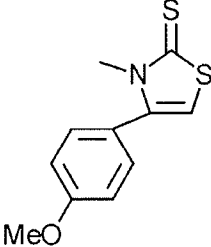
TABLE 2

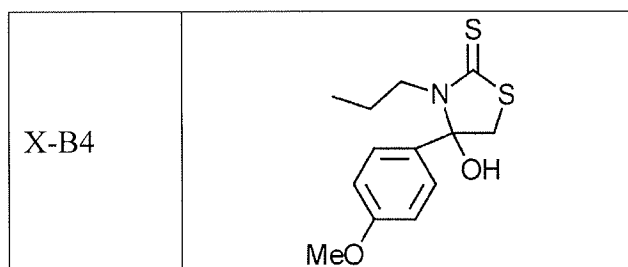
Reference	Compound
X-010	
X-105	
X-106	

X-107	
X-108	
X-109	
X-110	
X-111	
X-112	
X-113	
X-114	

X-115	
X-116	
X-120	
X-127	
X-131	
X-135	
X-136	
X-137	
X-142	

X-145	
X-149	
X-150	
X-151	
X-154	
X-156	
X-157	
X-167	
X-169	

X-179	
X-181	
X-182	
X-184	
X-185	
X-194	
X-195	
X-211	
X-B2	



[0091] The term “imidazole 2-thiones”, as used herein, refers to compositions having the general structural formula (I) and/or general structural formula (II) as described above, in which group X is S and group Y is NH.

[0092] The term “imidazole 2-ones”, as used herein, refers to compositions having the general structural formula (I) and/or general structural formula (II) as described above, in which group X is O and group Y is NH.

[0093] The term “thiazole 2-thiones”, as used herein, refers to compositions having the general structural formula (I) and/or general structural formula (II) as described above, in which group X is S and group Y is S.

[0094] The term “thiazole 2-ones”, as used herein, refers to compositions having the general structural formula (I) and/or general structural formula (II) as described above, in which group X is O and group Y is S.

[0095] As used herein, the term “aliphatic” includes both saturated and unsaturated, straight chain (i.e., unbranched) or branched aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, “aliphatic” is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl moieties. Thus, as used herein, the term “alkyl” includes straight and branched alkyl groups. An analogous convention applies to other generic terms such as “alkenyl”, “alkynyl” and the like. Furthermore, as used herein, the terms “alkyl”, “alkenyl”, “alkynyl” and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, “lower alkyl” may be used to indicate alkyl groups (substituted, unsubstituted, branched or unbranched) having from 1 to 6 carbon atoms.

[0096] In certain embodiments, the alkyl, alkenyl, and alkynyl groups described herein contain from 1 to 10 aliphatic carbon atoms. In other embodiments, the alkyl, alkenyl, and alkynyl groups described herein contain from 1 to 8 aliphatic carbon atoms. In still other

embodiments, the alkyl, alkenyl, and alkynyl groups described herein contain from 1 to 6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups described herein contain from 1 to 4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, *n*-propyl, isopropyl, allyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, *tert*-pentyl, *n*-hexyl, *sec*-hexyl, moieties and the like, which optionally may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

[0097] As used herein, the term “alicyclic” refers to compounds which combine the properties of aliphatic and cyclic compounds and include but are not limited to monocyclic, or polycyclic aliphatic hydrocarbons and bridged cycloalkyl compounds, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, “alicyclic” is intended herein to include, but is not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, which are optionally substituted with one or more functional groups. Illustrative alicyclic groups thus include, but are not limited to, for example, cyclopropyl, $-\text{CH}_2$ -cyclopropyl, cyclobutyl, $-\text{CH}_2$ -cyclobutyl, cyclopentyl, $-\text{CH}_2$ -cyclopentyl, cyclohexyl, $-\text{CH}_2$ -cyclohexyl, cyclohexenylethyl, cyclohexanylethyl, norbornyl moieties and the like, which optionally may bear one or more substituents.

[0098] As used herein, the term “alkoxy” or “alkyloxy” refers to a saturated (i.e., *O*-alkyl) or unsaturated (i.e., *O*-alkenyl and *O*-alkynyl) group attached to the parent molecular moiety through an oxygen atom. In certain embodiments, the alkyl group contains from 1 to 10 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains from 1 to 8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains from 1 to 6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains from 1 to 4 aliphatic carbon atoms. Examples of alkoxy, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *i*-butoxy, *sec*-butoxy, *tert*-butoxy, neopentoxy, *n*-hexoxy and the like.

[0099] As used herein, the term “thioalkyl” refers to a saturated (i.e., *S*-alkyl) or unsaturated (i.e., *S*-alkenyl and *S*-alkynyl) group attached to the parent molecular moiety through a sulfur atom. In certain embodiments, the alkyl group contains from 1 to 10 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains from 1 to 8 aliphatic carbon atoms. In still

other embodiments, the alkyl group contains from 1 to 6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains from 1 to 4 aliphatic carbon atoms. Examples of thioalkyl include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

[0100] The term “alkylamino” refers to a group having the structure —NHR' wherein R' is alkyl, as defined herein. The term “aminoalkyl” refers to a group having the structure NH₂R'—, wherein R' is alkyl, as defined herein. In certain embodiments, the alkyl group contains from 1 to 10 aliphatic carbon atoms. In yet other embodiments, the alkyl groups contain from 1 to 8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains from 1 to 6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains from 1 to 4 aliphatic carbon atoms. Examples of alkylamino include, but are not limited to, methylamino, ethylamino, isopropylamino and the like.

[0101] Some examples of substituents of the above-described aliphatic (and other) moieties of compounds described herein include, but are not limited to aliphatic; alicyclic; heteroaliphatic; heterocyclic; aromatic; heteroaromatic; aryl; heteroaryl; alkylaryl; heteroalkylaryl; alkylheteroaryl; heteroalkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; —OH; —NO₂; —CN; —CF₃; —CH₂CF₃; —CHCl₂; —CH₂OH; —CH₂CH₂OH; —CH₂NH₂; —CH₂SO₂CH₃; —C(O)R^X; —CO₂(R^X); —CON(R^X)₂; —OC(O)R^X; —OCO₂R^X; —OCON(R^X)₂; —N(R^X)₂; —S(O)₂R^X; —NR^X(CO)R^X, wherein each occurrence of R^X independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents described above herein and may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aryl or heteroaryl substituents described above herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described below.

[0102] In general, the terms “aromatic moiety” as used herein refer to a stable monocyclic or polycyclic, unsaturated moiety having preferably from 3 to 14 carbon atoms, each of which may be substituted or unsubstituted. In certain embodiments, the terms “aromatic moiety” refer to a planar ring having p-orbitals perpendicular to the plane of the ring at each ring atom and satisfying the Hückel rule where the number of pi electrons in the ring is (4*n* + 2), where *n*

is an integer. A monocyclic or polycyclic, unsaturated moiety that does not satisfy one or all of these criteria for aromaticity is defined herein as “non-aromatic” and is encompassed by the term “alicyclic.”

[0103] In general, the term “heteroaromatic moiety” as used herein refers to a stable monocyclic or polycyclic, unsaturated moiety having preferably from 3 to 14 carbon atoms, each of which may be substituted or unsubstituted; and comprising at least one heteroatom selected from O, S, and N within the ring (*i.e.*, in place of a ring carbon atom). In certain embodiments, the term “heteroaromatic moiety” refers to a planar ring comprising at least one heteroatom, having p-orbitals perpendicular to the plane of the ring at each ring atom, and satisfying the Hückel rule where the number of pi electrons in the ring is $(4n + 2)$, where n is an integer.

[0104] It should be appreciated that aromatic and heteroaromatic moieties, as defined herein may be attached via an alkyl or heteroalkyl moiety and thus also include, as non-limiting examples: $-(\text{alkyl})\text{-aromatic}$, $-(\text{heteroalkyl})\text{-aromatic}$, $-(\text{heteroalkyl})\text{-heteroaromatic}$, and $-(\text{heteroalkyl})\text{-heteroaromatic}$ moieties. Thus, as used herein, the phrases “aromatic or heteroaromatic moieties” and “aromatic, heteroaromatic, $-(\text{alkyl})\text{-aromatic}$, $-(\text{heteroalkyl})\text{-aromatic}$, $-(\text{heteroalkyl})\text{-heteroaromatic}$, and $-(\text{heteroalkyl})\text{-heteroaromatic}$ ” are interchangeable. Substituents include, but are not limited to, any of the previously mentioned substituents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound.

[0105] As used herein, the term “aryl” does not differ significantly from the common meaning of the term in the art, and refers to an unsaturated cyclic moiety comprising at least one aromatic ring. In certain embodiments, “aryl” refers to a monocyclic or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

[0106] As used herein, the term “heteroaryl” does not differ significantly from the common meaning of the term in the art, and refers to a cyclic aromatic radical having from 5 to 10 ring atoms of which one ring atom is selected from S, O, and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl,

oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

[0107] It should be appreciated that aryl and heteroaryl groups (including bicyclic aryl groups) can be unsubstituted or substituted, wherein substitution includes replacement of one or more of the hydrogen atoms thereon independently with any one or more of the following moieties including, but not limited to: aliphatic; alicyclic; heteroaliphatic; heterocyclic; aromatic; heteroaromatic; aryl; heteroaryl; alkylaryl; heteroalkylaryl; alkylheteroaryl; heteroalkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; $-\text{OH}$; $-\text{NO}_2$; $-\text{CN}$; $-\text{CF}_3$; $-\text{CH}_2\text{CF}_3$; $-\text{CHCl}_2$; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{CH}_2\text{OH}$; $-\text{CH}_2\text{NH}_2$; $-\text{CH}_2\text{SO}_2\text{CH}_3$; $-\text{C}(\text{O})\text{R}^{\text{X}}$; $-\text{CO}_2(\text{R}^{\text{X}})$; $-\text{CON}(\text{R}^{\text{X}})_2$; $-\text{OC}(\text{O})\text{R}^{\text{X}}$; $-\text{OCO}_2\text{R}^{\text{X}}$; $-\text{OCON}(\text{R}^{\text{X}})_2$; $-\text{N}(\text{R}^{\text{X}})_2$; $-\text{S}(\text{O})\text{R}^{\text{X}}$; $-\text{S}(\text{O})_2\text{R}^{\text{X}}$; $-\text{NR}^{\text{X}}(\text{CO})\text{R}^{\text{X}}$ wherein each occurrence of R^{X} independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aromatic, heteroaromatic, aryl, heteroaryl, $-(\text{alkyl})\text{aryl}$ or $-(\text{alkyl})\text{heteroaryl}$ substituents described above and herein may be substituted or unsubstituted. Additionally, it will be appreciated, that any two adjacent groups taken together may represent a 4-membered, 5-membered, 6-membered, or 7-membered substituted or unsubstituted alicyclic or heterocyclic moiety. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0108] As used herein, the term “cycloalkyl” refers specifically to groups having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of aliphatic, alicyclic, heteroaliphatic or heterocyclic moieties, may optionally be substituted with substituents including, but not limited to aliphatic; alicyclic; heteroaliphatic; heterocyclic; aromatic; heteroaromatic; aryl; heteroaryl; alkylaryl; heteroalkylaryl; alkylheteroaryl; heteroalkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; $-\text{OH}$; $-\text{NO}_2$; $-\text{CN}$; $-\text{CF}_3$; $-\text{CH}_2\text{CF}_3$; $-\text{CHCl}_2$; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{CH}_2\text{OH}$; $-\text{CH}_2\text{NH}_2$; $-\text{CH}_2\text{SO}_2\text{CH}_3$; $-\text{C}(\text{O})\text{R}^{\text{X}}$; $-\text{CO}_2(\text{R}^{\text{X}})$; $-\text{CON}(\text{R}^{\text{X}})_2$; $-\text{OC}(\text{O})\text{R}^{\text{X}}$; $-\text{OCO}_2\text{R}^{\text{X}}$; $-\text{OCON}(\text{R}^{\text{X}})_2$; $-\text{N}(\text{R}^{\text{X}})_2$; $-\text{S}(\text{O})\text{R}^{\text{X}}$; $-\text{S}(\text{O})_2\text{R}^{\text{X}}$;

$-\text{NR}^{\text{X}}(\text{CO})\text{R}^{\text{X}}$ wherein each occurrence of R^{X} independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aromatic, heteroaromatic, aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0109] As used herein, the term “heteroaliphatic” refers to aliphatic moieties in which one or more carbon atoms in the main chain have been substituted with a heteroatom. Thus, a heteroaliphatic group refers to an aliphatic chain which contains one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be linear or branched, and saturated or unsaturated. In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more moieties including, but not limited to aliphatic; alicyclic; heteroaliphatic; heterocyclic; aromatic; heteroaromatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; $-\text{OH}$; $-\text{NO}_2$; $-\text{CN}$; $-\text{CF}_3$; $-\text{CH}_2\text{CF}_3$; $-\text{CHCl}_2$; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{CH}_2\text{OH}$; $-\text{CH}_2\text{NH}_2$; $-\text{CH}_2\text{SO}_2\text{CH}_3$; $-\text{C}(\text{O})\text{R}^{\text{X}}$; $-\text{CO}_2(\text{R}^{\text{X}})$; $-\text{CON}(\text{R}^{\text{X}})_2$; $-\text{OC}(\text{O})\text{R}^{\text{X}}$; $-\text{OCO}_2\text{R}^{\text{X}}$; $-\text{OCON}(\text{R}^{\text{X}})_2$; $-\text{N}(\text{R}^{\text{X}})_2$; $-\text{S}(\text{O})\text{R}^{\text{X}}$; $-\text{S}(\text{O})_2\text{R}^{\text{X}}$; $-\text{NR}^{\text{X}}(\text{CO})\text{R}^{\text{X}}$ wherein each occurrence of R^{X} independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aromatic, heteroaromatic, aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0110] As used herein, the term “heterocycloalkyl,” “heterocycle,” or “heterocyclic” refers to compounds that combine the properties of heteroaliphatic and cyclic compounds and

include, but are not limited to, saturated and unsaturated mono- or polycyclic cyclic ring systems having from 5 to 16 atoms, wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may optionally be oxidized), wherein the ring systems are optionally substituted with one or more functional groups, as defined herein. In certain embodiments, the term “heterocycloalkyl”, “heterocycle” or “heterocyclic” refers to a non-aromatic 5-membered, 6-membered, or 7-membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally be oxidized), including, but not limited to, a bicyclic or tricyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds and each 7-membered ring has 0 to 3 double bonds; (ii) the nitrogen and sulfur heteroatoms may optionally be oxidized; (iii) the nitrogen heteroatom may optionally be quaternized; and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative heterocycles include, but are not limited to, heterocycles such as furanyl, thiofuranyl, pyranal, pyrrolal, thienal, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, dioxazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, triazolyl, thiatriazolyl, oxatriazolyl, thiadiazolyl, oxadiazolyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, dithiazolyl, dithiazolidinyl, tetrahydrofuryl, and benzofused derivatives thereof.

[0111] In certain embodiments, a “substituted heterocycle, or heterocycloalkyl or heterocyclic” group is utilized and as used herein, refers to a heterocycle, or heterocycloalkyl or heterocyclic group, as defined above, substituted by the independent replacement of one, two or three of the hydrogen atoms thereon with groups including but not limited to aliphatic; alicyclic; heteroaliphatic; heterocyclic; aromatic; hetero aromatic; aryl; heteroaryl; alkylaryl; heteroalkylaryl; alkylheteroaryl; hetero alkylhetero aryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; -NO₂; -CN; -CF₃; -CH₂CF₃; -CHCl₂; -CH₂OH; -CH₂CH₂OH; -CH₂NH₂; -CH₂SO₂CH₃; -C(O)R^X; -CO₂(R^X); -CON(R^X)₂; -OC(O)R^X; -OCO₂R^X; -OCON(R^X)₂; -N(R^X)₂; -S(O)R^X; -S(O)₂R^X; -NR^X (CO)R^X wherein each occurrence of R^X independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents

described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aromatic, heteroaromatic, aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples, which are described herein.

[0112] Additionally, it should be appreciated that any of the alicyclic or heterocyclic moieties described above and herein may comprise an aryl or heteroaryl moiety fused thereto. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0113] As used herein, the terms “halo” and “halogen” refer to an atom selected from fluorine, chlorine, bromine and iodine.

[0114] As used herein, the term “haloalkyl” denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

[0115] As used herein, the term “amino” refers to a primary amine ($-\text{NH}_2$), a secondary amine ($-\text{NHR}^X$), a tertiary amine ($-\text{NR}^X\text{R}^Y$), or a quaternary amine ($-\text{N}^+\text{R}^X\text{R}^Y\text{R}^Z$), where R^X , R^Y , and R^Z are independently an aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic or heteroaromatic moiety, as defined herein. Examples of amino groups include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

[0116] As used herein, the term “ $\text{C}_1\text{--C}_6$ alkylidene” refers to a substituted or unsubstituted, linear or branched, saturated divalent radical consisting solely of carbon and hydrogen atoms, having from one to six carbon atoms, having a free valence “—” at both ends of the radical.

[0117] As used herein, the term “ $\text{C}_2\text{--C}_6$ alkenylidene” refers to a substituted or unsubstituted, linear or branched, unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to six carbon atoms, having a free valence “—” at both ends of the radical, and wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule.

[0118] As used herein, the terms “aliphatic,” “heteroaliphatic,” “alkyl,” “alkenyl,” “alkynyl,” “heteroalkyl,” “heteroalkenyl,” “heteroalkynyl,” and the like encompass substituted and unsubstituted, saturated and unsaturated, and linear and branched groups. Similarly, the

terms “alicyclic,” “heterocyclic,” “heterocycloalkyl,” “heterocycle” and the like encompass substituted and unsubstituted, and saturated and unsaturated groups. Additionally, the tetras “cycloalkyl,” “cycloalkenyl,” “cycloalkynyl,” “heterocycloalkyl,” “heterocycloalkenyl,” “heterocycloalkynyl,” “aromatic,” “heteroaromatic,” “aryl,” “heteroaryl” and the like encompass both substituted and unsubstituted groups.

[0119] The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include: aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include: salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When a compound is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include: acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *p*-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids. Thus, representative pharmaceutically acceptable salts include but are not limited to acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexyl-resorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, *N*-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate,

sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. It will be understood that, as used herein, the compounds referred to herein are meant to also include the pharmaceutically acceptable salts.

[0120] It is understood that certain embodiments herein encompass the use of pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents. As used herein, the term “solvate” or “salt solvated” refers to a complex of variable stoichiometry formed by a solute (such as compounds of Formula (I) or (II) described below (or a salt thereof)) and a solvent. In some embodiments, such solvents do not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. In illustrative embodiments, the solvent is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol, and acetic acid. In one particular embodiment, the solvent is water, providing a “hydrate.”

[0121] In embodiments, the term “IC₅₀” refers to an inhibitor concentration at which an enzyme, such as, *e.g.*, GSK-3, exhibits 50% of its maximal activity. In other embodiments, the term ““IC₅₀” refers to an inhibitor concentration at which expression of mRNA and/or protein is inhibited by 50%.

[0122] The terms “treat”, “treatment”, and “treating” refer to prophylactically avoiding and/or prolonging the development or acquisition of, reducing the risk of developing, delaying acquisition of, inhibiting the development or progression of, stabilizing, and/or causing regression of a disease, disorder or symptom thereof.

[0123] The term “GSK-3 mediated disorder” refers to a disease and/or condition which relies on the activity of GSK-3 for expression of the disease and/or condition. For example, in embodiments, a GSK-3 mediated disorder may include all diseases and/or conditions relying on the activity of GSK-3 for expression thereof which are treatable with lithium and/or other known GSK-3 inhibitors.

[0124] Depending upon the context of use, the term “subject in need thereof” as used herein, refers to a subject at risk for developing a disease, disorder, and/or symptom thereof, a subject exhibiting symptoms associated with a disease, disorder, and/or symptom thereof, and/or a subject having a disease, disorder, and/or symptom thereof. For example, a subject in

need thereof may include a subject at risk for developing a GSK-3 mediated disorder and/or symptom thereof, a subject exhibiting symptoms associated with a GSK-3 mediated disorder, and/or a subject having a GSK-3 disorder. In some embodiments, a subject in need thereof includes a subject having a pathology brought about or cause at least in part by aberrant activity of GSK-3.

[0125] The terms “administer”, “administration”, and “administering” as used herein, refers to systemic use, such as by injection (*e.g.*, parenterally), intravenous infusion, suppositories and oral administration thereof, and/or to topical use of the imidazole and/or thiazole compounds and, more specifically, imidazole 2-thiones, imidazole 2-ones, thiazole 2-thiones, and/or thiazole 2-ones, and pharmaceutical compositions including the same.

[0126] As used herein, the term “compatible” with regard to components of a composition means that components of the composition are capable of being comingled without interacting in a manner which would substantially decrease the efficacy of the pharmaceutically active compound under ordinary use conditions.

[0127] The term “patient”, as used herein, is intended to encompass any mammal, animal or human subject, which may benefit from treatment with the compounds, compositions and methods of the present invention, and includes children and adults.

[0128] The term “pharmaceutically acceptable” as used herein, refers to a pharmaceutically active agent and/or other agents/ingredients for use in a pharmaceutical composition which are not deleterious to a subject receiving the pharmaceutical composition and/or which are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like commensurate with a reasonable benefit/risk ratio.

[0129] As used herein, the term “pharmaceutical carrier” denotes a solid or liquid filler, diluent or encapsulating substance. These materials are well known to those skilled in the pharmaceutical arts. Some examples of the substances that can serve as pharmaceutical carriers include sugars, such as lactose, glucose, and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols, such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; agar; alginic acid; pyrogen-free water; isotonic

saline; and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants, such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, tableting agents, and preservatives, can also be present. Formulation of the components into pharmaceutical compositions is done using conventional techniques.

[0130] Embodiments of the present disclosure relate to methods for modulating GSK-3 activity, to methods for modulating GSK-3 signaling, to methods for treating GSK-3 mediated disorders, and to pharmaceutical compositions for GSK-3 activity, modulating GSK-3 signaling, and/or treating GSK-3 mediated disorders. Embodiments of the methods for modulating GSK-3 activity will now be described in detail. Thereafter, embodiments of methods for modulating GSK-3 signaling, methods for treating GSK-3 mediated disorders, and pharmaceutical compositions will be described in detail.

I. Methods for Modulating GSK-3 Activity

[0131] Based on molecular assay results, the compounds of General Formula (I) and General Formula (II) (*i.e.*, the imidazole and/or thiazole compounds) are believed to modulate, such as, *e.g.*, to inhibit, GSK-3 activity. Methods for modulating, such as, *e.g.*, inhibiting, GSK-3 activity in a cell expressing GSK-3 are disclosed. Such methods may include contacting a cell expressing GSK-3 with a therapeutically effective amount of at least one imidazole and/or thiazole compound (*i.e.*, at least one imidazole compound and/or thiazole compound) and, more specifically, at least one imidazole 2-thione, imidazole 2-one, thiazole 2-thione, and/or thiazole 2-one, to the subject, or pharmaceutically-acceptable salts or solvates thereof. The imidazole and/or thiazole compounds referenced herein are as previously described. In embodiments, the methods include contacting the cell with a therapeutically effective amount of the imidazole and/or thiazole compounds. In particular embodiments, the method includes contacting the cell with a therapeutically effective amount of COB-152, COB-187, COB-197, and/or COB-198.

[0132] In embodiments, contacting a cell expressing GSK-3 with a therapeutically effective amount of imidazole and/or thiazole compounds is effective to modulate, such as, *e.g.*, to inhibit, activity of at least one of GSK-3 α (*i.e.*, GSK-3 alpha) or GSK-3 β (*i.e.*, GSK-3 beta). In some embodiments, contacting the cell expressing GSK-3 with a therapeutically effective amount of the imidazole and/or thiazole compounds modulates the activity of GSK-3 by inhibiting the GSK-3 activity. In further embodiments, contacting the cell expressing GSK-3

with the therapeutically effective amount of the imidazole and/or thiazole compounds is effective to inhibit the activity of at least one of GSK-3, including GSK-3 α and/or GSK-3 β , by about 20% to about 100%, or by about 30% to about 95%, or by about 40% to about 90%, or by about 50% to about 85%, or by about 60% to about 80%, or by about 75%. In embodiments, the activity of GSK-3 modulated, such as, *e.g.*, inhibited, by the imidazole and/or thiazole compounds is a phosphorylation activity.

[0133] In embodiments, the imidazole and/or thiazole compounds have an IC₅₀ value for GSK-3 of from about 100 pM to about 50 μ M, or from about 1 nM to about 25 μ M, or from about 10 nM to about 10 μ M, or from about 25 nM to about 1 μ M, or from about 50 nM to about 500 nM, or from about 75 nM to about 250 nM, or from about 100 nM to about 200 nM, or about 150 nM. In some embodiments, the imidazole and/or thiazole compounds have an IC₅₀ value for GSK-3 in the nanomolar range. In other embodiments, a cell expressing GSK-3 is contacted with imidazole and/or thiazole compounds which are provided in a concentration of from about 100 pM to about 50 μ M, or from about 1 nM to about 25 μ M, or from about 10 nM to about 1 μ M, or from about 50 nM to about 500 nM, or about 75 nM.

[0134] In embodiments, the imidazole and/or thiazole compounds are specific for GSK-3. More particularly, the imidazole and/or thiazole compounds may be specific for GSK-3 such that the imidazole and/or thiazole compounds preferentially recognize and/or bind to GSK-3 in a complex mixture of proteins, enzymes, and/or macromolecules. In embodiments, the imidazole and/or thiazole compounds preferentially recognize, bind to, and/or otherwise combine with GSK-3 in a complex mixture such that the imidazole and/or thiazole compounds have limited to no effect on non-GSK-3 kinases. For example, in embodiments, the imidazole and/or thiazole compounds preferentially recognize, bind, and/or otherwise combine with GSK-3 such that the activity thereof is inhibited by at least about 75%, and the imidazole and/or thiazole compounds recognize, bind, and/or otherwise combine with non-GSK-3 kinases such that less than about 70% of the activity thereof is inhibited. In further embodiments, the imidazole and/or thiazole compounds bind non-GSK-3 kinases such that less than about 50%, or less than about 40%, or less than about 30%, or less than about 20% of the activity thereof is inhibited.

[0135] In specific embodiments, the non-GSK-3 kinases are cyclin-dependent protein kinases (*i.e.*, CDK's), including but not limited to, CDK1, CDK2, CDK5/p25, CDK5/p35, CDK7, CDK8, CDK9 Cyclin K, CDK9 Cyclin T1, and combination thereof. In further

embodiments, the imidazole and/or thiazole compounds have limited to no effect on CDK's, such that upon contact therewith less than about 20% of the activity thereof is inhibited.

[0136] In embodiments, contacting a cell expressing GSK-3 with the imidazole and/or thiazole compounds is effective to modulate signaling of GSK-3. GSK-3 is involved in a wide range of signal transduction cascades (*i.e.*, signaling pathways) involving cellular processes, including, *e.g.*, glycogen metabolism, cell development, gene transcription, protein translation, cytoskeletal organization, cell cycle regulation, proliferation, and apoptosis. GSK-3 acts as a downstream regulatory switch for numerous signaling pathways, including cellular responses to WNT, growth factors, insulin, receptor tyrosine kinases (*i.e.*, RTK's), Hedgehog pathways, and g-protein coupled receptors (*i.e.*, GPCR's). Additionally, GSK-3 can be part of a multiprotein complex that includes the proteins axis inhibitor (*i.e.*, AXIN), adenomatous polyposis coli (*i.e.*, APC), casein kinase-1 (*i.e.*, CSNK1), and β -catenin (*i.e.*, β -Ctnn). GSK-3 has been shown to phosphorylate β -catenin, targeting it for ubiquitination and subsequent degradation.

[0137] Thus, in some embodiments, the imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that phosphorylation of substrates thereof, such as, *e.g.*, β -catenin, is reduced. In embodiments, contacting a cell expressing GSK-3 with imidazole and/or thiazole compounds is effective to modulate signaling of GSK-3, such that expression of β -catenin is enhanced (further demonstrating inhibition of GSK-3). In other embodiments, contacting a cell expressing GSK-3 with imidazole and/or thiazole compounds is effective to enhance expression of β -catenin. More particularly, in embodiments, contacting a cell expressing GSK-3, such as, *e.g.*, a macrophage, with imidazole and/or thiazole compounds is effective to enhance protein expression of β -catenin. Thus, it is believed that imidazole and/or thiazole compounds may be effective to enhance protein expression of β -catenin by inhibiting GSK-3 activity at the post-transcriptional level.

[0138] GSK-3 is also involved in signaling pathways in the innate immune response, including those affecting cytokine production. Thus, in embodiments, contacting a cell expressing GSK-3 with thiazole and/or imidazole compounds is effective to modulate signaling of GSK-3 such that immune products of Toll-like receptor (*i.e.*, TLR) signaling, such as, *e.g.*, cytokines, are suppressed. For example, GSK-3 has been shown to modulate the function of lipopolysaccharide (*i.e.*, LPS), an inducer of signal transduction events in TLR signaling.

[0139] Thus, in some embodiments, imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that function of LPS and/or A β is inhibited. More particularly, in embodiments, imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that LPS- and/or A β -induced expression of reactive products (*e.g.*, cytokines), such as, *e.g.*, expression of i-nitric oxide synthase (*i.e.*, iNOS), Interleukin 6, (*i.e.*, IL-6), Tumor Necrosis Factor- α (*i.e.*, TNF- α), Interleukin 1 β (*i.e.*, IL-1 β), Interleukin 1 α (*i.e.*, IL-1 α), Interferon β (*i.e.*, IFN- β), and/or Interferon γ (*i.e.*, IFN- γ) is inhibited. In further embodiments, the imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that expression, such as, *e.g.*, LPS- and/or A β -induced expression, of iNOS, IL-6, TNF- α , IL-1 β , IL-1 α , IFN- β , and/or IFN- γ is suppressed. In other embodiments, the imidazole and/or thiazole compounds are effective to inhibit LPS-induced and/or A β -induced expression of reactant products to suppress expression of iNOS, IL-6, and TNF- α . In some embodiments, such suppression of reactive products (*e.g.*, cytokines) is effected by imidazole and/or thiazole compounds in a dose-dependent manner. Such suppression of reactive products (*e.g.*, cytokines) may be observed via suppression of mRNA and/or protein expression thereof.

[0140] In embodiments, the methods for modulating, such as, *e.g.*, inhibiting, GSK-3 activity are performed by contacting a sample having a cell expressing GSK-3 with a therapeutically effective amount of imidazole and/or thiazole compounds. In further embodiments, the methods for modulating GSK-3 activity are performed by contacting the cell expressing GSK-3 with a therapeutically effective amount of the imidazole and/or thiazole compounds *in vitro* and/or *ex vivo*. In embodiments, the cells expressing GSK-3 employed in the methods disclosed herein include eukaryotic cells (as GSK-3 may be ubiquitously expressed in all eukaryotes). In further embodiments, the cells expressing GSK-3 employed in the methods disclosed herein include mammalian cells. More specifically, cells expressing GSK-3 may be human, non-human primate, canine, feline, murine, bovine, equine, porcine, and/or lagomorph. In further embodiments, the methods for inhibiting cells expressing GSK-3 are performed by contacting at least one of solid tumor cells, blood cancer cells, leukocytes (*e.g.*, macrophages and/or lymphocytes), hepatocytes, endothelial cells, adipocytes, skeletal muscle cells, or pancreatic cells with a therapeutically effective amount of the imidazole and/or thiazole compounds.

[0141] In other embodiments, the methods for modulating, such as, *e.g.*, inhibiting, GSK-3 activity are performed by contacting a cell expressing GSK-3 with a therapeutically effective

amount of the imidazole and/or thiazole compounds *in vivo*. In such embodiments, the imidazole and/or the thiazole compounds may be administered to a subject in need thereof.

[0142] Embodiments of the methods for modulating, such as, *e.g.*, inhibiting, GSK-3 activity have been described in detail. Further embodiments directed to methods for modulating GSK-3 signaling will now be described.

II. Methods for Modulating GSK-3 Signaling

[0143] Based on molecular assay results, the compounds of General Formula (I) and General Formula (II) (*i.e.*, the imidazole and/or thiazole compounds) are believed to modulate, such as, *e.g.*, to inhibit, GSK-3 signaling. Methods for modulating GSK-3 signaling in a cell expressing GSK-3 are disclosed. Such methods may include contacting a cell expressing GSK-3 with a therapeutically effective amount of at least one imidazole and/or thiazole compound (*i.e.*, at least one imidazole compound and/or thiazole compound) and, more specifically, at least one imidazole 2-thione, imidazole 2-one, thiazole 2-thione, and/or thiazole 2-one, to the subject, or pharmaceutically-acceptable salts or solvates thereof. The imidazole and/or thiazole compounds referenced herein are as previously described. In embodiments, the methods include contacting the cell with a therapeutically effective amount of the imidazole and/or thiazole compounds. In particular embodiments, the method includes contacting the cell with a therapeutically effective amount of COB-152, COB-187, COB-197, and/or COB-198. In embodiments, a cell expressing GSK-3 is contacted with imidazole and/or thiazole compounds which are provided in a concentration of from about 100 pM to about 50 μ M, or from about 1 nM to about 25 μ M, or from about 10 nM to about 1 μ M, or from about 50 nM to about 500 nM, or about 75 nM.

[0144] In embodiments, contacting a cell expressing GSK-3 with the imidazole and/or thiazole compounds is effective to modulate signaling of GSK-3, as previously described, such as, *e.g.*, in the various signaling cascades in which GSK-3 is involved. For example, in some embodiments, the imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that phosphorylation of substrates thereof, such as, *e.g.*, β -catenin, is reduced. In further embodiments, contacting a cell expressing GSK-3 with imidazole and/or thiazole compounds is effective to modulate signaling of GSK-3 such that expression of β -catenin is enhanced (further demonstrating inhibition of GSK-3).

[0145] For example, in embodiments, imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that function of LPS is inhibited. More particularly, in embodiments, imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that LPS induction of reactive products (such as, *e.g.*, iNOS, IL-6, TNF- α , IL-1 β , IL-1 α , IFN- β , and/or IFN- γ) is inhibited. In further embodiments, the imidazole and/or thiazole compounds are effective to modulate signaling of GSK-3 such that expression of iNOS, IL-6, TNF- α , IL-1 β , IL-1 α , IFN- β , and/or IFN- γ is suppressed. In some embodiments, such suppression of reactive products (*e.g.*, cytokines) is effected by imidazole and/or thiazole compounds in a dose-dependent manner. Such suppression of reactive products (*e.g.*, cytokines) may be observed via suppression of mRNA and/or protein expression thereof.

[0146] In embodiments, the methods for modulating GSK-3 signaling are performed by contacting a sample having a cell expressing GSK-3 with a therapeutically effective amount of imidazole and/or thiazole compounds. In further embodiments, the methods for modulating GSK-3 signaling are performed by contacting the cell expressing GSK-3 with a therapeutically effective amount of the imidazole and/or thiazole compounds *in vitro* and/or *ex vivo*. In embodiments, the cells expressing GSK-3 employed in the methods disclosed herein include eukaryotic cells (as GSK-3 may be ubiquitously expressed in all eukaryotes). In further embodiments, the cells expressing GSK-3 employed in the methods disclosed herein include mammalian cells. More specifically, cells expressing GSK-3 may be human, non-human primate, canine, feline, murine, bovine, equine, porcine, and/or lagomorph. In further embodiments, the methods for modulating GSK-3 signaling are performed by contacting at least one of solid tumor cells, blood cancer cells, leukocytes (*e.g.*, macrophages and/or lymphocytes), hepatocytes, endothelial cells, adipocytes, skeletal muscle cells, or pancreatic cells with a therapeutically effective amount of the imidazole and/or thiazole compounds.

[0147] In other embodiments, the methods for modulating GSK-3 signaling are performed by contacting a cell expressing GSK-3 with a therapeutically effective amount of the imidazole and/or thiazole compounds *in vivo*. In such embodiments, the imidazole and/or the thiazole compounds may be administered to a subject in need thereof.

[0148] Embodiments of the methods for modulating GSK-3 signaling have been described in detail. Further embodiments directed to methods for treating GSK-3-mediated disorders will now be described.

III. Methods for Treatment of GSK-3 Mediated Disorders

[0149] Methods for treating GSK-3 mediated disorders in a subject in need thereof are disclosed. Such methods may include administering a therapeutically effective amount of at least one imidazole and/or thiazole compound and, more specifically, at least one imidazole 2-thione, imidazole 2-one, thiazole 2-thione, and/or thiazole 2-one, to the subject, or pharmaceutically-acceptable salts or solvates thereof, wherein administration of the imidazole and/or thiazole compound is effective to treat the GSK-3 mediated disorder. The imidazole and/or thiazole compounds referenced herein are as previously described. In embodiments, the method includes administering imidazole and/or thiazole compounds to the subject. In particular embodiments, the method includes administering a therapeutically effective amount of COB-152, COB-187, COB-197, and/or COB-198 to the subject.

[0150] As previously discussed, GSK-3 plays a vital role in signal transduction activity, wherein it is involved in a wide range of signal transduction cascades involving cellular processes, including, *e.g.*, glycogen metabolism, cell development, gene transcription, protein translation, cytoskeletal organization, cell cycle regulation, proliferation, and apoptosis. Thus, GSK-3 is germane to a plethora of cellular processes. Consequently, dysfunctional GSK-3 is a component of a host of pathological processes, as well as a major therapeutic target. While GSK-3 was first identified as a serine/threonine kinase regulating glycogen synthase (*i.e.*, GS) via phosphorylation causing inactivation thereof (thus having a role in glucose metabolism), GSK-3 has since been identified as a kinase for over 40 proteins and has been shown to play a role in numerous cellular and/or physiological processes, such as, *e.g.*, embryogenesis, inflammation, and neuroplasticity.

[0151] Additionally, aberrant GSK-3 activity, and specifically, GSK-3 over-activity, has been implicated in a variety of disorders and/or diseases, including but not limited to, malaria, cancer, insulin resistance, type 2 diabetes mellitus, muscle wasting, neurodegenerative diseases, cardiovascular diseases, myocardial diseases, pathological inflammation, bone diseases, renal diseases, HIV-related neurological disorders, horse colic, sepsis, and shock. Moreover, aberrant GSK-3 activity, and specifically, GSK-3 over-activity, has also been implicated in psychiatric and central nervous system (*i.e.*, CNS) diseases. As a result, agents for inhibition of GSK-3 activity have been actively sought.

[0152] In embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders and/or diseases chosen from malaria, cancer,

insulin resistance, type 2 diabetes mellitus, muscle wasting (*i.e.*, muscle atrophy), neurodegenerative disease, cardiovascular disease, myocardial disease, pathological inflammation, bone disease, renal disease, human immunodeficiency virus (*i.e.*, HIV)-related neurological disorder, sepsis, toxic shock, psychiatric disease, CNS disease, or combination thereof.

[0153] In embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a cancer chosen from leukemia, pancreatic cancer, multiple myeloma, glioblastoma, or combination thereof. In further embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a leukemia chosen from acute myeloid leukemia (*i.e.*, AML), chronic myeloid leukemia (*i.e.*, CML), acute lymphocytic leukemia (*i.e.*, ALL), chronic lymphocytic leukemia (*i.e.*, CLL), or combination thereof. In particular embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is acute lymphoblastic leukemia.

[0154] In other embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a pancreatic cancer chosen from exocrine group pancreatic cancer, endocrine group pancreatic cancer, or combination thereof. In further embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is an exocrine group pancreatic cancer chosen from pancreatic adenocarcinoma, acinar cell carcinoma of the pancreas, cystadenocarcinomas, pancreatoblastoma, pancreatic mucinous cystic neoplasms, or combination thereof. In other embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a pancreatic neuroendocrine tumor (*i.e.*, PET).

[0155] In other embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is multiple myeloma. In yet other embodiments, the imidazole and/or thiazole compounds are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is glioblastoma.

[0156] In embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a

neurodegenerative disease chosen from Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, amyotrophic lateral sclerosis (*i.e.*, ALS), or combination thereof.

[0157] In embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a cardiovascular disease chosen from atherosclerosis, cardiac ischemia, cardiac reperfusion injury, cardiac hypertrophy, or combination thereof. In other embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is chosen from cardiac hypertrophy, rheumatic heart disease, hypertensive heart disease, ischemic heart disease (*i.e.*, coronary artery disease), cerebrovascular disease, inflammatory heart disease, atherosclerosis, ischemia, reperfusion injury, coronary artery disease, peripheral artery disease, carotid artery disease, myocarditis, inflammation of the myocardium, or combination thereof.

[0158] In other embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a pathological inflammation chosen from acne, asthma, autoimmune diseases, autoinflammatory diseases, celiac disease, chronic prostatitis, glomerulonephritis, hypersensitivities, inflammatory bowel diseases, pelvic inflammatory diseases, reperfusion injury, rheumatoid arthritis, sarcoidosis, transplant rejection, vasculitis, interstitial cystitis, or combination thereof.

[0159] In embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a bone disease chosen from bone spur, bone tumor, craniosynostosis, coffin-lowry syndrome, fibrodysplasia ossificans progressiva, fibrous dysplasia, fong disease, fracture, giant cell tumor of bone, greenstick fracture, hypophosphatasia, klippel-feil syndrome, metabolic bone disease, multiple myeloma, nail-patella syndrome, osteoarthritis, osteitis deformans, osteitis fibrosa cystica, osteitis pubis, condensing osteitis, osteochondritis dissecans, osteochondroma, osteogenesis imperfecta, osteomalacia, osteomyelitis, osteopenia, osteopetrosis, osteoporosis, porotic hyperostosis, primary hyperparathyroidism, proteus syndrome, renal osteodystrophy, salter-harris fractures, water on the knee, or combination thereof.

[0160] In other embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a renal disease chosen from parenchymal renal disease, proliferative renal disease, or combination thereof. In other embodiments, the imidazole and/or thiazole compounds

described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is chosen from Alport Syndrome, amyloidosis and kidney disease, glomerular disease, goodpasture syndrome, horseshoe kidney, IgA nephropathy, lupus nephritis, nephrotic syndrome, nephrotic syndrome in adults, renal dysplasia and cystic disease, renal tubular acidosis, renovascular disease, solitary kidney, or combination thereof.

[0161] In other embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is an HIV-related neurological disorder chosen from dementia, viral infections, fungal and parasitic infections, neuropathy, vacuolar myelopathy, psychological conditions, lymphomas, neurosyphilis, or combination thereof. In further embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is neuroAIDS.

[0162] In embodiments, the imidazole and/or thiazole compounds described herein are effective to treat GSK-3 mediated disorders, wherein the GSK-3 mediated disorder is a CNS disease chosen from mood disorders, bipolar disorders, cognitive impairments, schizophrenia, depression, catalepsy, epilepsy, encephalitis, meningitis, migraine, topical spastic paraparesis, arachnoid cysts, Huntington's Disease, Alzheimer's Disease, attention deficit/hyperactivity disorder (*i.e.*, ADHD), Locked-in Syndrome, Parkinson's Disease, Tourett's, multiple sclerosis, or combination thereof.

[0163] In other embodiments, the methods for treating GSK-3 mediated disorders include systemic administration of the imidazole and/or thiazole compounds, or pharmaceutically-acceptable salts or solvates thereof. The systemic administration of the imidazole and/or thiazole compounds may be selected from the group consisting of oral, sublingual, subcutaneous, intravenous, intramuscular, intranasal, intrathecal, intraperitoneal, percutaneous, intranasal, and enteral administration, and combinations thereof. In one or more particular embodiments, the systemic administration of the imidazole and/or thiazole compounds is oral.

[0164] In other embodiments, the methods for treating GSK-3 mediated disorders include administration of at least one imidazole and/or thiazole compound, or pharmaceutically-acceptable salts or solvates thereof, to a subject in need thereof in a dose of from about 0.1 mg/kg to about 20 mg/kg, or from about 0.3 mg/kg to about 15 mg/kg, or from about 1 mg/kg to about 10 mg/kg, or from about 3 mg/kg to about 10 mg/kg, or from about 5 mg/kg to about 10 mg/kg. It is contemplated that such doses serve as non-limiting examples of suitable doses

of imidazole and/or thiazole compounds for a subject in need thereof. In one or more particular embodiments, at least one imidazole and/or thiazole compound is administered to a subject in need thereof in a dose of about 1 mg/kg. In further embodiments, the dose of imidazole and/or thiazole compounds is administered daily. In still further embodiments, the dose of imidazole and/or thiazole compounds is administered at least once a day. In yet still a further embodiment, the dose of imidazole and/or thiazole compounds is administered more often than one time a day; for example, the dose of imidazole and/or thiazole compounds is administered at least two times a day, at least three times a day, at least four times a day, at least five times a day, and/or at least six times a day.

[0165] In one or more embodiments, the methods for treating the GSK-3 mediated disorder include administration of at least one imidazole and/or thiazole compound, or pharmaceutically-acceptable salts or solvates thereof, to a subject in need thereof, wherein the subject is a mammal. In one or more particular embodiments, the subject is a mammal chosen from humans, non-human primates, canines, felines, murines, bovines, equines, porcines, and lagomorphs.

[0166] In other embodiments, the methods for treating GSK-3 mediated disorder in a subject in need thereof further include monitoring disease development and/or progression and repeating administration of imidazole and/or thiazole compounds (or pharmaceutically-acceptable salts or solvates thereof) one or more times, thereby treating the GSK-3 mediated disorder. Development and/or progression of the GSK-3 mediated disorder can be monitored in a variety of ways known to the skilled clinician. In embodiments, if the appropriate assessment indicates that the GSK-3 mediated disorder is developing, progressing, and/or has not yet responded to treatment, a clinician may administer an additional dose of at least one imidazole and/or thiazole compound. The clinician may then reassess disease development and/or progression. Successive rounds of administering imidazole and/or thiazole compounds coupled with monitoring development and/or progression of the GSK-3 mediated disorder, may be necessary in order to achieve the desired treatment of the GSK-3 mediated disorder.

[0167] Embodiments of the methods for treating a GSK-3 mediated disorder have been described in detail. Further embodiments of pharmaceutical compositions for modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases will now be described.

IV. Pharmaceutical Compositions for Modulation of GSK-3 Activity, Modulation of GSK-3 Signaling, and/or Treatment of GSK-3 Mediated Disorders

[0168] Pharmaceutical compositions for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases are disclosed herein and may be employed in the methods previously described. In one or more embodiments, a pharmaceutical composition including at least one imidazole and/or thiazole compound, or a pharmaceutically-acceptable salt or solvate thereof, as an active agent (*i.e.*, an active ingredient) is disclosed. In other embodiments, a pharmaceutical composition including the imidazole and/or thiazole compounds as an active agent is disclosed, wherein the imidazole and/or thiazole compound is formulated for administration to a subject for the inhibition of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders. The imidazole and/or thiazole compounds referenced herein are as previously described. In embodiments, the pharmaceutical composition includes a therapeutically effective amount of one or more imidazole and/or thiazole compounds.

[0169] In some embodiments, the provided pharmaceutical compositions do not contain any of the compounds listed in **TABLE 2**. In some embodiments, the provided pharmaceutical compositions include one or more compounds listed in **TABLE 2**. In some embodiments, the provided pharmaceutical compositions include one or more compounds listed in **TABLE 2** in combination with one or more compounds listed in **TABLE 1**.

[0170] In other embodiments, the pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases further includes an additional active agent. In embodiments, the pharmaceutical composition for the modulation, such as, *e.g.*, the inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases further includes a therapeutically effective amount of an additional active agent for the treatment of conditions associated with modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases. For example, the pharmaceutical composition may further include an additional active agent for the treatment of leukemia, pancreatic cancer, multiple myeloma, glioblastoma, Parkinson's Disease, Alzheimer's Disease, ALS, atherosclerosis, cardiac ischemia, cardiac reperfusion injury, cardiac hypertrophy, sepsis, toxic shock,

parenchymal renal disease, proliferative renal disease, neuroAIDS, bipolar disorder, mood disorder, schizophrenia, depression, or combination thereof.

[0171] In some embodiments, the pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases further includes a pharmaceutically acceptable carrier and/or excipient. Suitable pharmaceutically acceptable carriers may include a wide range of known diluents (*i.e.*, solvents), fillers, extending agents, adjuvants, binders, suspending agents, disintegrates, surfactants, lubricants, wetting agents, preservatives, stabilizers, antioxidants, antimicrobials, buffering agents and the like commonly used in this field. Such carriers may be used singly or in combination according to the form of the pharmaceutical preparation. In further embodiments, a preparation resulting from the inclusion of a pharmaceutically acceptable carrier may incorporate, if necessary, one or more solubilizing agents, buffers, preservatives, colorants, perfumes, flavorings and the like, as widely used in the field of pharmaceutical preparation.

[0172] Examples of suitable excipients include water, saline, Ringer's solution, dextrose solution, and solutions of ethanol, glucose, sucrose, dextran, mannose, mannitol, sorbitol, polyethylene glycol (*i.e.*, PEG), phosphate, acetate, gelatin, collagen, Carbopol®, and vegetable oils. A full discussion of pharmaceutically acceptable excipients is provided in Remington's Pharmaceutical Sciences I (Mack Pub. Co.), the contents of which are incorporated by reference herein. Examples of suitable adjuvants include inorganic compounds (*e.g.*, aluminum hydroxide, aluminum phosphate, calcium phosphate hydroxide, and beryllium), mineral oil (*e.g.*, paraffin oil), bacterial products (*e.g.*, killed bacteria *Bordetella pertussis*, *Mycobacterium bovis*, and toxoids), nonbacterial organics (*e.g.*, squalene and thimerosal), delivery systems (*e.g.*, detergents (Quil A)), cytokines (*e.g.*, IL-1, IL-2, and IL-12), and combinations (*e.g.*, Freund's complete adjuvant, Freund's incomplete adjuvant). Examples of suitable preservatives, stabilizers, antioxidants, antimicrobials, and buffering agents include BHA, BHT, citric acid, ascorbic acid, tetracycline, and the like. Cream or ointment bases useful in formulation include lanolin, Silvadene® (Marion), Aquaphor® (Duke Laboratories).

[0173] In embodiments, the pharmaceutical composition for modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases includes at least one imidazole and/or thiazole compound,

or a pharmaceutically-acceptable salt or solvate thereof, formulated into a dosage form. In one or more particular embodiments, at least one imidazole and/or thiazole compound is formulated into a dosage form selected from the group consisting of creams, emulsions, ointments, gels, tablets, capsules, granules, pills, injections, solutions, suspensions, and syrups. The form and administration route for such pharmaceutical composition are not limited and can be suitably selected. For example, tablets, capsules, granules, pills, syrups, solutions, emulsions, and suspensions may be administered orally. Additionally, injections (*e.g.*, subcutaneous, intravenous, intramuscular, and intraperitoneal) may be administered intravenously either singly or in combination with a conventional replenisher containing glucose, amino acid and/or the like, or may be singly administered intramuscularly, intracutaneously, subcutaneously and/or intraperitoneally.

[0174] A pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases may be prepared according to methods known in the pharmaceutical field using a pharmaceutically acceptable carrier. For example, oral forms such as tablets, capsules, granules, pills and the like are prepared according to known methods using excipients such as saccharose, lactose, glucose, starch, mannitol and the like; binders such as syrup, gum arabic, sorbitol, tragacanth, methylcellulose, polyvinylpyrrolidone and the like; disintegrates such as starch, carboxymethylcellulose or the calcium salt thereof, microcrystalline cellulose, polyethylene glycol and the like; lubricants such as talc, magnesium stearate, calcium stearate, silica and the like; and wetting agents such as sodium laurate, glycerol and the like.

[0175] In some embodiments, the pharmaceutical compositions may include targeted or non-targeted carriers such as liposomes, particles made from biodegradable particles, polymersomes, or ultrasound bubbles, for example. The compounds of General Formula (I) or (II) may be incorporated into the either non-targeted or targeted carriers. For the targeted particles, the targeting could be via a ligand attached to the particles, whereby the ligand is specific for a moiety overexpressed at the site of disease. Alternatively, when carriers are not present, the compounds of General Formula (I) or (II) may be conjugated to the targeting ligand directly to achieve the targeted delivery.

[0176] Injections, solutions, emulsions, suspensions, syrups and the like may be prepared according to known methods suitably using solvents for dissolving the active agent, such as ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol, polyethylene glycol,

sesame oil and the like; surfactants such as sorbitan fatty acid ester, polyoxyethylenesorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylene of hydrogenated castor oil, lecithin and the like; suspending agents such as cellulose derivatives including carboxymethylcellulose sodium, methylcellulose and the like, natural gums including tragacanth, gum arabic and the like; and preservatives such as parahydroxybenzoic acid esters, benzalkonium chloride, sorbic acid salts and the like.

[0177] In some embodiments, the pharmaceutical composition for modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases includes a packaging material suitable for the pharmaceutical composition and instructions for use of the pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases. In particular embodiments, the pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases is provided for administration to a subject in unit dose and/or multi-dose containers, *e.g.*, vials and/or ampoules. In specific embodiments, the pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases is provided for administration to a subject in a device including a reservoir. In further specific embodiments, the pharmaceutical composition for the modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases is provided for administration to a subject in a device including a reservoir which is a vial, wherein the device is a syringe.

[0178] The pharmaceutical compositions for the modulation, such as, *e.g.*, inhibition of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases as described herein may be contacted with a cell expressing GSK-3 and/or may be administered to a subject in need thereof, as described previously.

[0179] Embodiments of pharmaceutical compositions for modulation, such as, *e.g.*, inhibition, of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases have been described in detail.

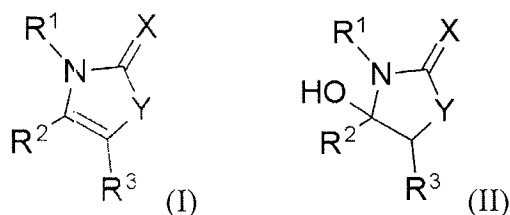
[0180] In some embodiments, at least one imidazole and/or thiazole compound, or a pharmaceutically-acceptable salt or solvate thereof, for use in the inhibition of GSK-3 activity,

modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases is/are disclosed. In embodiments, the imidazole and/or thiazole compound, or a pharmaceutically-acceptable salt or solvate thereof, may further include an additional active agent for the inhibition of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases, as previously described. In other embodiments, the imidazole and/or thiazole compound, or a pharmaceutically-acceptable salt or solvate thereof, are incorporated into a pharmaceutical composition for the inhibition of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases and/or are formulated into a dosage form for the inhibition of GSK-3 activity, modulation of GSK-3 signaling, and/or treatment of GSK-3 mediated disorders and/or diseases, as previously described. The imidazole and/or thiazole compounds referenced herein are as previously described.

[0181] Methods according to embodiments herein may find use in probing the molecular mechanisms of normal and abnormal cellular processes. Methods according to embodiments herein may find use in probing the molecular mechanisms of normal physiology and pathology. Methods according to embodiments herein may be used to engender normal physiology. Methods according to embodiments herein may be used to kill or diminish the presence of microbes. Methods according to embodiments herein may be used to aid the processing of valuable products from biological sources. Methods according to embodiments herein may be a component of a diagnostic or prognostic assay.

[0182] It should now be understood that various aspects of the present disclosure are described herein and that such aspects may be utilized in conjunction with various other aspects.

[0183] In a first aspect, a method for modulating glycogen synthase kinase-3 (GSK-3) activity in a cell expressing GSK-3 is disclosed. The method includes contacting the cell with a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which: R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH ; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0184] In a second aspect, a method according to the first aspect is disclosed, wherein the contacting is effective to modulate the activity of at least one of GSK-3 α or GSK-3 β in the cell.

[0185] In a third aspect, a method according to the first or the second aspect is disclosed, wherein the activity of GSK-3 is modulated by inhibiting the activity thereof.

[0186] In a fourth aspect, a method according to the first to the third aspects is disclosed, wherein the activity of GSK-3 is modulated by inhibiting the activity thereof by at least about 50%.

[0187] In a fifth aspect, a method according to the first to the fourth aspects is disclosed, wherein the activity of GSK-3 is modulated by inhibiting the activity thereof by at least about 75%.

[0188] In a sixth aspect, a method according to the first to the fifth aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is provided in a concentration of from about 1 nM to about 50 μ M.

[0189] In a seventh aspect, a method according to the first to the sixth aspects is disclosed, wherein the activity of GSK-3 is modulated by inhibiting the activity thereof, and wherein at least one compound of General Formula (I) or (II) has an IC_{50} value of from about 100 pM to about 50 μ M.

[0190] In an eighth aspect, a method according to the first to the seventh aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is specific for GSK-3.

[0191] In a ninth aspect, a method according to the first to the eighth aspects is disclosed, wherein the contacting is effective to modulate signaling of GSK-3.

[0192] In a tenth aspect, a method according to the first to the ninth aspects is disclosed, wherein the contacting is effective to enhance expression of β -catenin.

[0193] In an eleventh aspect, a method according to the first to the tenth aspects is disclosed, wherein the contacting is effective to inhibit function of lipopolysaccharide (LPS).

[0194] In a twelfth aspect, a method according to the first to the eleventh aspects is disclosed, wherein the contacting is effective to suppress expression of at least one of i-Nitrous-Oxide Synthase (iNOS), Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α), Interleukin 1 β (IL-1 β), Interleukin 1 α (IL-1 α), Interferon β (IFN- β), or Interferon γ (IFN- γ).

[0195] In a thirteenth aspect, a method according to the first to the twelfth aspects is disclosed, wherein the contacting is effected *in vitro*.

[0196] In a fourteenth aspect, a method according to the first to the twelfth aspects is disclosed, wherein the contacting is effected *in vivo*.

[0197] In a fifteenth aspect, a method according to the first to the fourteenth aspects is disclosed, wherein the activity of GSK-3 is a phosphorylation activity.

[0198] In a sixteenth aspect, a method according to the first to the fifteenth aspects is disclosed, wherein the cell is a mammalian cell.

[0199] In a seventeenth aspect, a method according to the first to the sixteenth aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is a thiazole 2-thione.

[0200] In an eighteenth aspect, a method according to the first to the seventeenth aspects is disclosed, wherein: R³ is -H; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

[0201] In a nineteenth aspect, a method according to the first to the eighteenth aspects is disclosed, wherein R¹ is chosen from C₁ to C₄ aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted

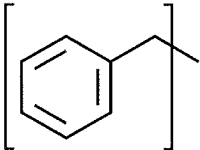
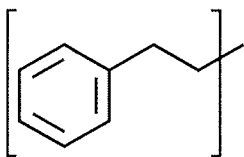
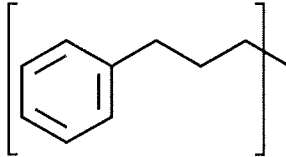
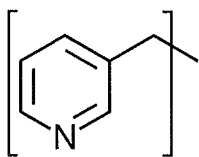
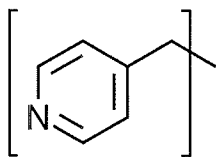
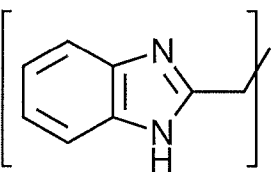
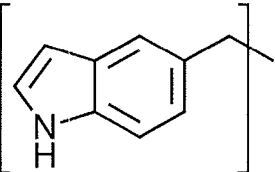
heteroaryl groups, or combination thereof; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

[0202] In a twentieth aspect, a method according to the first to the nineteenth aspects is disclosed, wherein R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

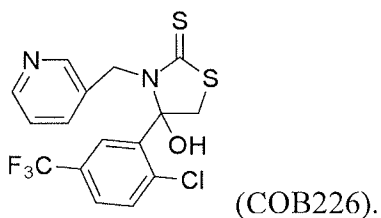
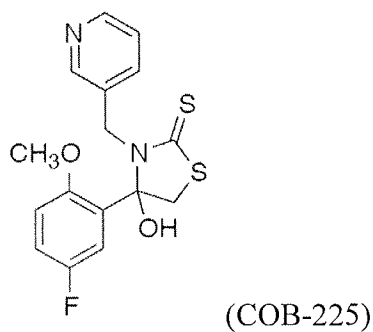
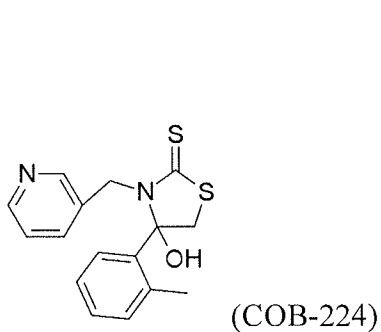
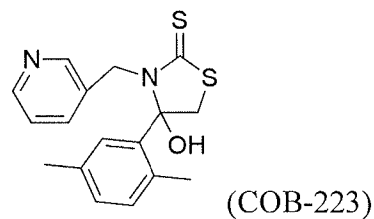
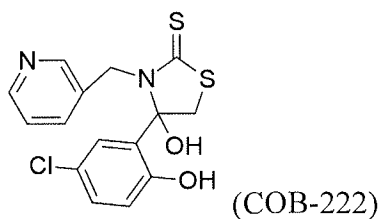
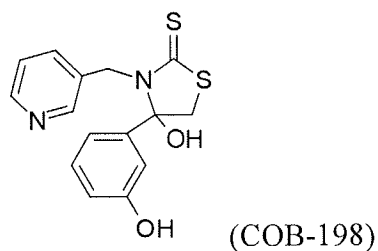
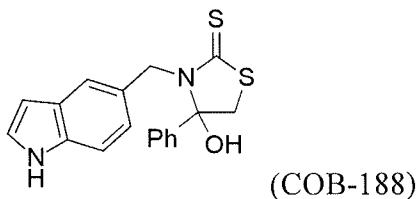
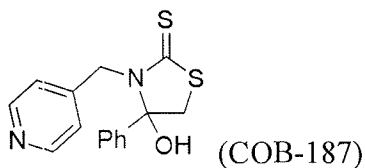
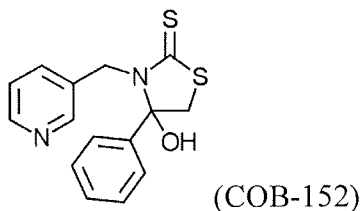
[0203] In a twenty-first aspect, a method according to the first to the twentieth aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

[0204] In a twenty-second aspect, a method according to the first to the twenty-first aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic groups optionally substituted with heteroaryl groups in which one or more ring atoms is N, or combination thereof; R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

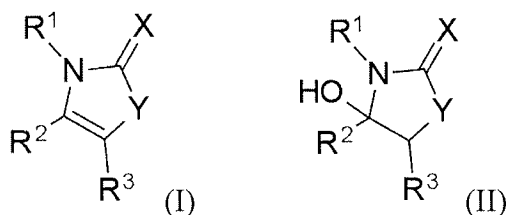
[0205] In a twenty-third aspect, a method according to the first to the twenty-first aspects is

disclosed, wherein R^1 is chosen from methyl, ethyl, propyl, butyl, 2-propenyl, , , , , , , or  in the at least one compound of General Formula (I) or (II).

[0206] In a twenty-fourth aspect, a method according to the first to the twenty-third aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:



[0207] In a twenty-fifth aspect, a method for modulating glycogen synthase kinase-3 (GSK-3) signaling is disclosed. The method includes contacting a cell expressing GSK-3 with a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which: R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O; and Y is S or NH; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0208] In a twenty-sixth aspect, a method according to the twenty-fifth aspect is disclosed, wherein the contacting is effective to modulate signaling of GSK-3, resulting in at least one of enhanced expression of β -catenin, inhibited function of lipopolysaccharide (LPS), or suppressed expression of i-Nitrous-Oxide Synthase (iNOS), Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α), Interleukin 1 β (IL-1 β), Interleukin 1 α (IL-1 α), Interferon β (IFN- β), and/or Interferon γ (IFN- γ).

[0209] In a twenty-seventh aspect, a method according to the twenty-fifth or the twenty-sixth aspect is disclosed, wherein the at least one compound of General Formula (I) or (II) is a thiazole 2-thione.

[0210] In a twenty-eighth aspect, a method according to the twenty-fifth to the twenty-seventh aspects is disclosed, wherein: R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

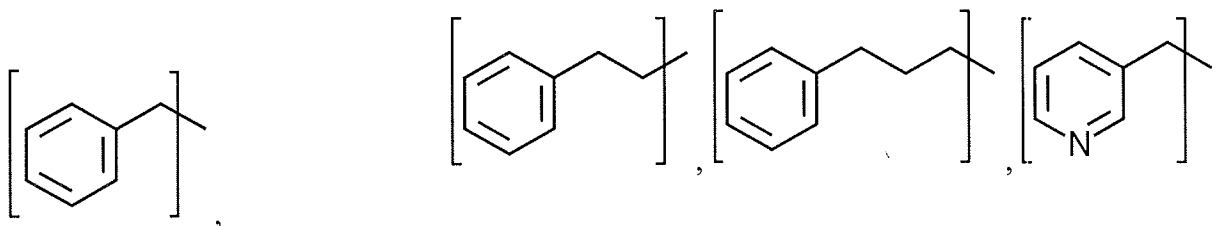
[0211] In a twenty-ninth aspect, a method according to the twenty-fifth to the twenty-eighth aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

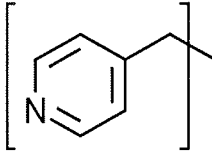
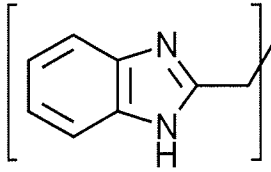
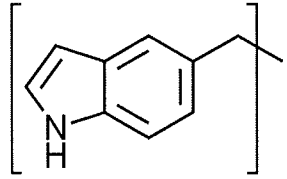
[0212] In a thirtieth aspect, a method according to the twenty-fifth to the twenty-ninth aspects is disclosed, wherein R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

[0213] In a thirty-first aspect, a method according to the twenty-fifth to the thirtieth aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

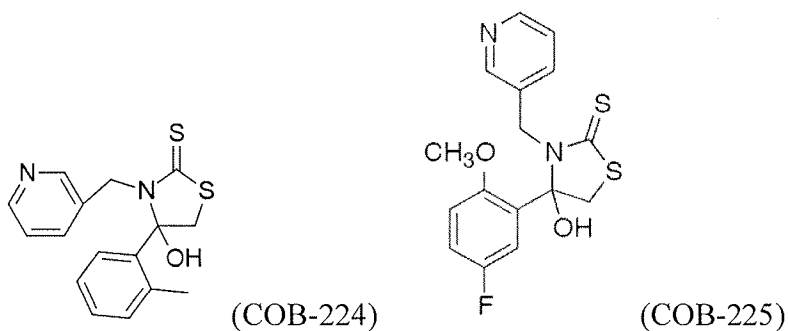
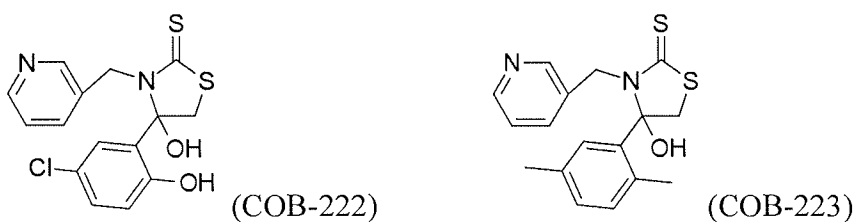
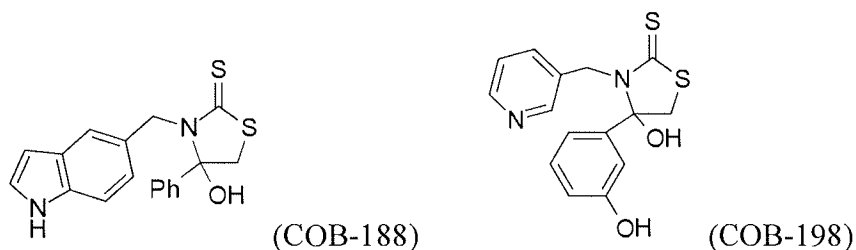
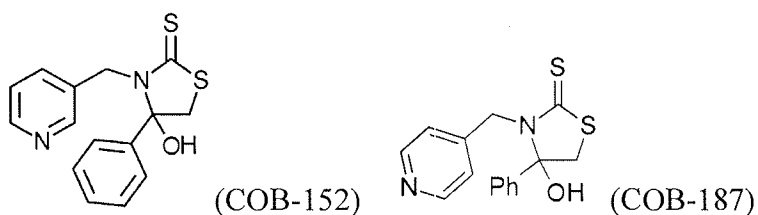
[0214] In a thirty-second aspect, a method according to the twenty-fifth to the thirty-first aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic groups optionally substituted with heteroaryl groups in which one or more ring atoms is N, or combination thereof; R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N; R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

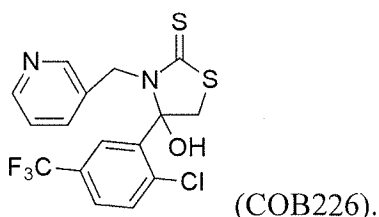
[0215] In a thirty-third aspect, a method according to the twenty-fifth to the thirty-first aspects is disclosed, wherein R^1 is chosen from methyl, ethyl, propyl, butyl, 2-propenyl,



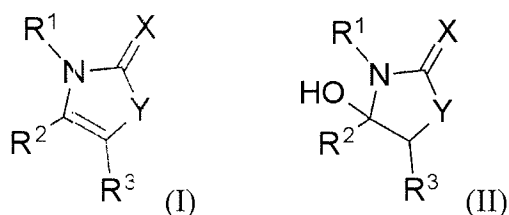


 , or 
 in the at least one compound of General Formula (I) or (II).

[0216] In a thirty-fourth aspect, a method according to the twenty-fifth to the thirty-third aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:





[0217] In a thirty-fifth aspect, a method for treating a GSK-3-mediated disorder in a subject in need thereof is disclosed. The method includes: administering to the subject a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which: R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH ; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0218] In a thirty-sixth aspect, a method according to the thirty-fifth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from malaria, cancer, insulin resistance, type 2 diabetes mellitus, muscle wasting, neurodegenerative disease, cardiovascular disease, myocardial disease, pathological inflammation, bone disease, renal disease, human immunodeficiency virus (HIV)-related neurological disorder, sepsis, toxic shock, psychiatric disease, central nervous system (CNS) disease, or combination thereof.

[0219] In a thirty-seventh aspect, a method according to the thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from leukemia, pancreatic cancer, multiple myeloma, glioblastoma, or combination thereof.

[0220] In a thirty-eighth aspect, a method according to the thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is acute lymphoblastic leukemia (ALL).

[0221] In a thirty-ninth aspect, a method according to thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis (ALS), or combination thereof.

[0222] In a fortieth aspect, a method according to thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from atherosclerosis, cardiac ischemia, cardiac reperfusion injury, cardiac hypertrophy, or combination thereof.

[0223] In a forty-first aspect, a method according to thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from sepsis, toxic shock, or combination thereof.

[0224] In a forty-second aspect, a method according to the thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from parenchymal renal disease, proliferative renal disease, or combination thereof.

[0225] In a forty-third aspect, a method according to the thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is neuroAIDS.

[0226] In a forty-fourth aspect, a method according to the thirty-fifth or the thirty-sixth aspect is disclosed, wherein the GSK-3 mediated disorder is chosen from bipolar disorder, mood disorder, schizophrenia, depression, or combination thereof.

[0227] In a forty-fifth aspect, a method according to the thirty-fifth to the forty-sixth aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is a thiazole 2-thione.

[0228] In a forty-sixth aspect, a method according to the thirty-fifth to the forty-fifth aspects is disclosed, wherein: R^3 is $-H$; X is S; and Y is S in the at least one compound of General Formula (I) or (II).

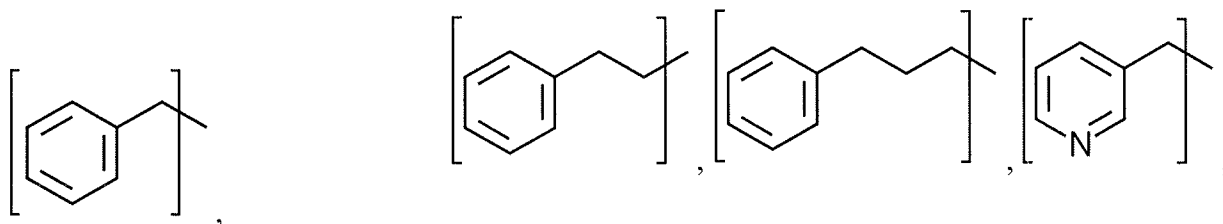
[0229] In a forty-seventh aspect, a method according to the thirty-fifth to the forty-sixth aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^3 is $-H$; X is S ; and Y is S in the at least one compound of General Formula (I) or (II).

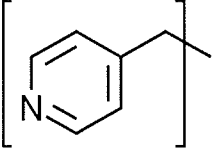
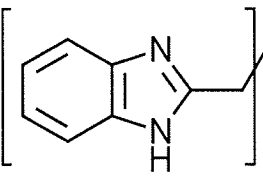
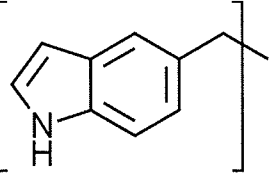
[0230] In a forty-eighth aspect, a method according to the thirty-fifth to the forty-seventh aspects is disclosed, wherein R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N ; R^3 is $-H$; X is S ; and Y is S in the at least one compound of General Formula (I) or (II).

[0231] In a forty-ninth aspect, a method according to the thirty-fifth to the forty-eighth aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N ; R^3 is $-H$; X is S ; and Y is S in the at least one compound of General Formula (I) or (II).

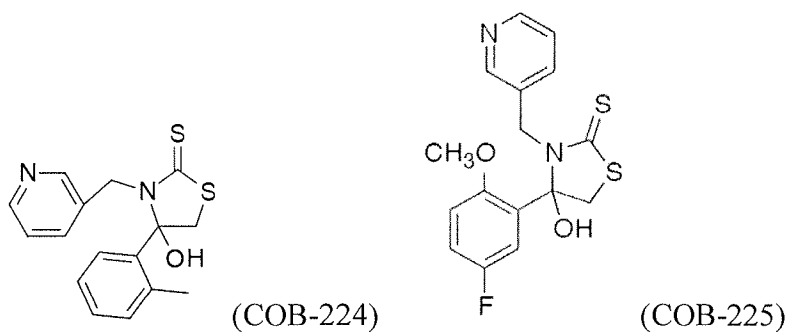
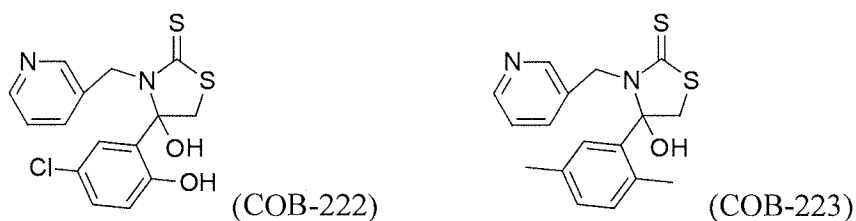
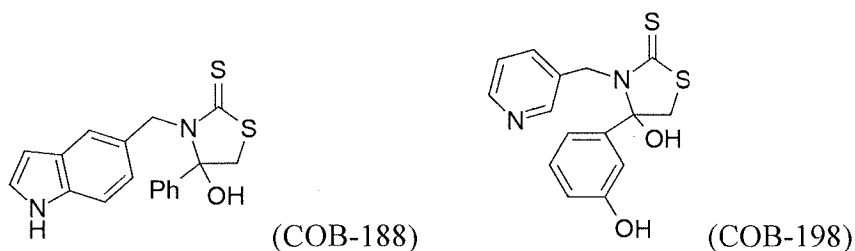
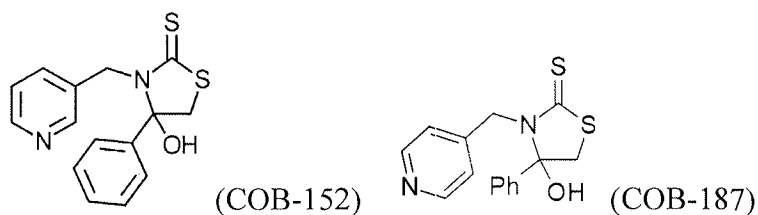
[0232] In a fiftieth aspect, a method according to the thirty-fifth to the forty-ninth aspects is disclosed, wherein R^1 is chosen from C_1 to C_4 aliphatic groups optionally substituted with heteroaryl groups in which one or more ring atoms is N , or combination thereof; R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N ; R^3 is $-H$; X is S ; and Y is S in the at least one compound of General Formula (I) or (II).

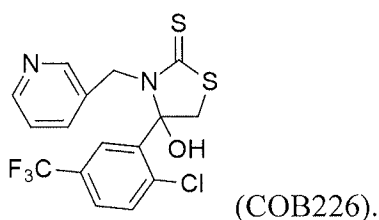
[0233] In a fifty-first aspect, a method according to the thirty-fifth to the forty-ninth aspects is disclosed, wherein R^1 is chosen from methyl, ethyl, propyl, butyl, 2-propenyl,





 , or 
 in the at least one compound of General Formula (I) or (II).

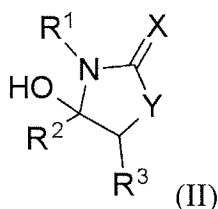
[0234] In a fifty-second aspect, a method according to the thirty-fifth to the fifty-first aspects is disclosed, wherein the at least one compound of General Formula (I) or (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:





[0235] In a fifty-third aspect, a method according to the thirty-fifth to the fifty-second aspects is disclosed, wherein the administering includes administering a pharmaceutical composition including the at least one compound of General Formula (I) or (II) in combination with at least one pharmaceutically-acceptable carrier.

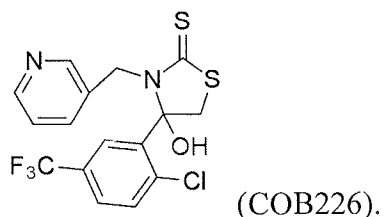
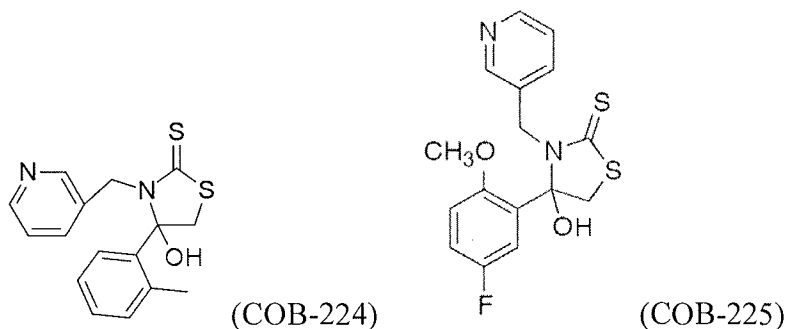
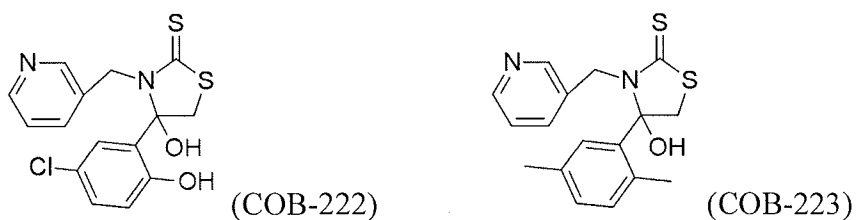
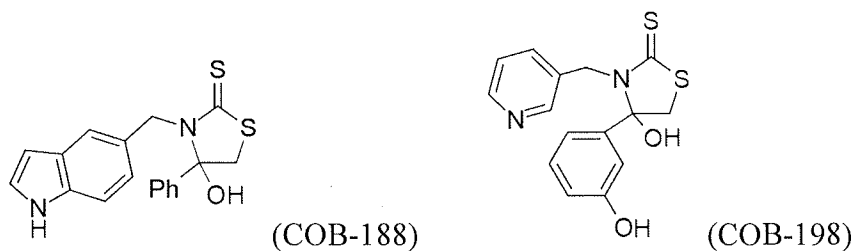
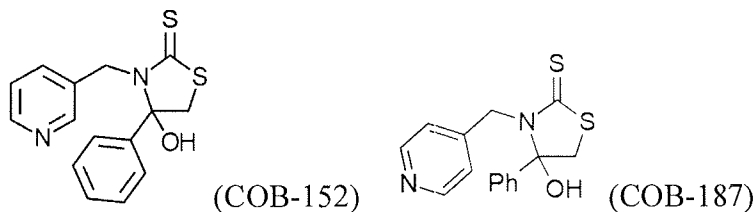
[0236] In a fifty-fourth aspect, a method for modulating glycogen synthase kinase-3 (GSK-3) activity in a cell expressing GSK-3 is disclosed, the method including: contacting the cell with a therapeutically effective amount of at least one compound of General Formula (II):



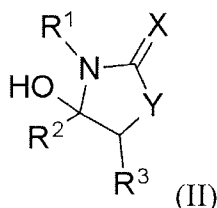
or a pharmaceutically-acceptable salt or solvate thereof, in which: R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH ; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0237] In a fifty-fifth aspect, a method according to the fifty-fourth aspect is disclosed, wherein the at least one compound of General Formula (II) is chosen from COB-152, COB-

187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:

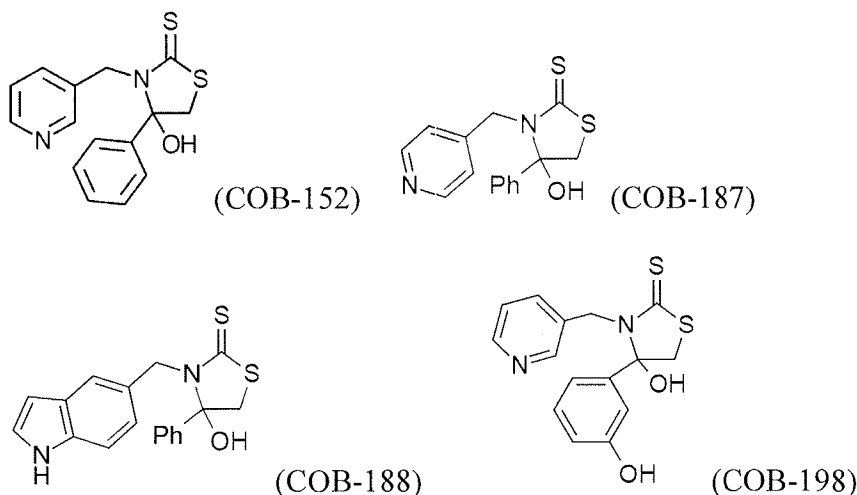


[0238] In a fifty-sixth aspect, a method for inhibiting glycogen synthase kinase-3 (GSK-3) activity in a cell expressing GSK-3 is disclosed, the method including: contacting the cell with a therapeutically effective amount of at least one compound of General Formula (II):

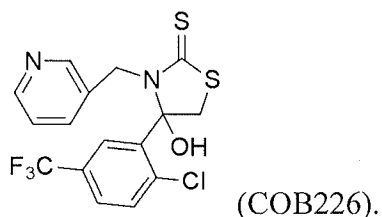
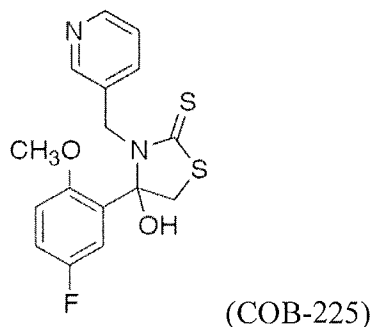
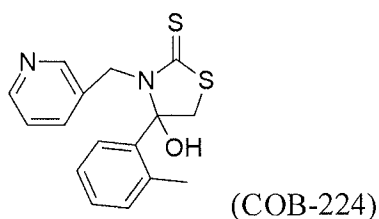
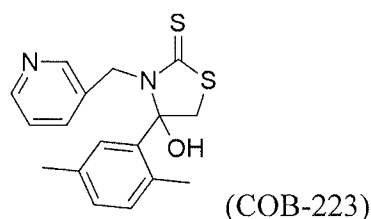
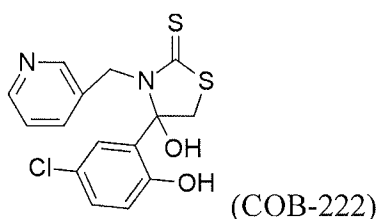


or a pharmaceutically-acceptable salt or solvate thereof, in which: R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin; R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof; X is S or O ; and Y is S or NH ; with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true: (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof; (b) R^1 is hexyl; (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

[0239] In a fifty-seventh aspect, a method according to the fifty-sixth aspect is disclosed, wherein the at least one compound of General Formula (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:



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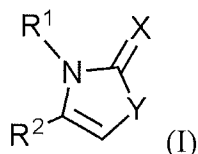
EXAMPLES

[0240] The embodiments described herein will be further clarified by the following examples. The exemplary compounds synthesized and/or characterized in the Examples to follow should be understood to be illustrative in nature and in no regard limiting to the scope of the General Formulas provided or of the methods described herein.

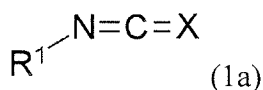
General Synthetic Methods

Synthetic Example 1

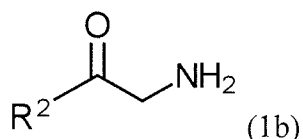
[0241] Compounds having General Formula (I):



in which X = O or S; Y = NH; R¹ and R² are as described above, may be synthesized by adding an isothiocyanate or isocyanate of formula (1a):

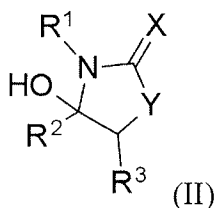


(100 mol%, X = O or S) and Et₃N (50 mol.%) to an EtOH (0.01 M) solution of a hydrochloride of a methylamino ketone of formula (1b) (100 mol.%):



to form a reaction mixture. The reaction mixture is heated at 140 °C for 20 min using microwave irradiation. The microwave irradiation may be carried out using an Initiator Biotage Microwave Synthesizer, for example, operating at 400 W, 2.45 GHz. The solvent is then removed by means of rotary evaporation, and the product is isolated by flash chromatography. The purification is performed by eluting the crude product with 5% to 10% ethyl acetate (EtOAc) in CH₂Cl₂ for imidazole-2-thiones (X = S) or with EtOAc for imidazole-2-ones (X = O). Yields for this general synthetic method are typically in the range of from 15% to 65%.

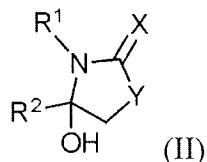
[0242] Additionally, compounds having General Formula (II):



in which X = O or S; Y = NH; and R¹, R², and R³ are as described above, may be synthesized by the above method by heating the reaction mixture at about 140 °C using means other than microwave irradiation. Without intent to be bound by theory, it is believed that microwave irradiation increases the rate of hydroxyl elimination, so as to favor formation of the compounds of General Formula (I) when the microwave irradiation is applied during heating.

Synthetic Example 2

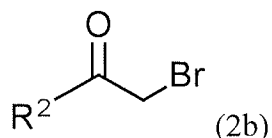
[0243] Compounds having General Formula (II):



in which $X = S$; $Y = S$; and R^1 and R^2 are as described above, may be synthesized by adding carbon disulfide (CS_2 ; 150 mol.%) and K_2CO_3 (50 mol.%) to a solution of an amine of the formula (2a):



(150 mol.%) in $H_2O:EtOH$ (0.2 M, 1:1) and then adding a 2-bromoketone derivative of formula (2b):



(100 mol%) to form a reaction mixture. The reaction mixture is stirred in an open flask at room temperature ($25\text{ }^{\circ}C \pm 2\text{ }^{\circ}C$) for 1 hour to 3 hours. Then, the crude reaction mixture is extracted with ethyl acetate ($EtOAc$; $3 \times 10\text{ mL}$), and the combined organic layers are dried over $MgSO_4$ and filtered. The solvent is evaporated by rotary evaporation. The product is isolated by flash chromatography using 10%-20% $EtOAc$ in hexanes. In some cases, some products may precipitate during the reaction. In such cases the product may be isolated by filtration, washed thoroughly with solvent ($EtOH:H_2O$, 1:1), then dried.

[0244] Compounds having General Formula (II), in which $X = O$; $Y = S$; and R^1 , R^2 , and R^3 are as described above may be synthesized by the above method by replacing the carbon disulfide (CS_2) with carbonyl sulfide ($C=O=S$; 150 mol.%).

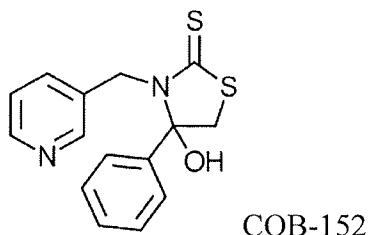
Synthetic Example 3

[0245] Compounds having General Formula (I), in which $X = O$ or S ; $Y = S$; and R^1 and R^2 are as described above, may be synthesized by dehydrating a compound having General Formula (II) prepared according to Synthetic Example 2 or by any other suitable method, in which groups R^1 , R^2 , X , and Y of the compound having General Formula (II) are the same as those in the desired compound having General Formula (I).

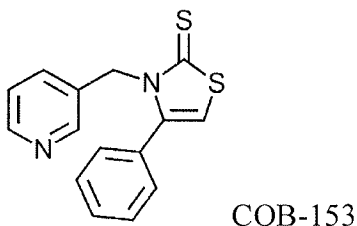
[0246] To perform the dehydration, to an ethanol solution containing 1 molar equivalent of a compound of General Formula (II), 1.2 molar equivalents of hydrochloric acid (1 M solution in ethyl acetate) are added to form a reaction mixture. The reaction mixture is submitted to microwave irradiation for 20 min at 140 °C. The solvent is removed by rotary evaporation. The crude product is purified by flash chromatography.

Exemplary Compounds

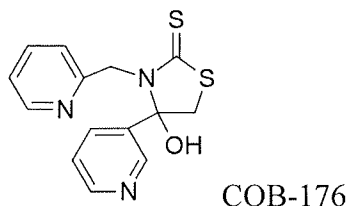
[0247] Except where noted otherwise, compounds having General Formula (I) or General Formula (II) were prepared according to one of the Synthetic Examples 1–3 above. Proton NMR (^1H -NMR) spectra were obtained using a Brüker Avance (300 MHz) spectrometer. Carbon NMR (^{13}C -NMR) spectra were obtained at 75 MHz. Chemical shifts are reported in ppm on the δ scale relative to deuterated chloroform ($CDCl_3$) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet, m = multiplet), coupling constant in Hz, integration. HPLC analyses were performed with a Shimadzu LC-10AT machine equipped with a UV detector by employing a reverse-phase Discovery-C8 (15 cm $\times$ 4.6 mm $\times$ 5 μ m; Supelco) column eluting with methanol (MeOH) in H_2O at 1 mL/min flow using the following protocol: 50% MeOH/ H_2O , 8 min; 90% MeOH/ H_2O , 5 min; 90% MeOH/ H_2O , 5 min; 50% MeOH/ H_2O , 3 min.



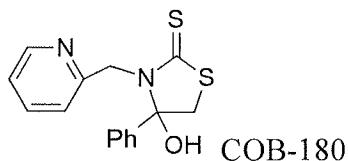
[0248] COB-152 was prepared according to Synthetic Example 2. Based on 33.8 mg of product recovered, the yield was 89%. For the COB-152, the following data were obtained: 33.8 mg (89%); R_f 0.4 (60% EtOAc in hexanes); t_R = 11.78 min; ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.36-8.35 (m, 2H, Py), 7.86 (s, 1H, OH), 7.59 (dt, J = 7.9 Hz, 1H, Py), 7.39-7.34 (m, 5H, Ph), 4.80 (d, J = 15 Hz, 1H, PyCHH), 4.52 (d, J = 15 Hz, 1H, PyCHH), 3.74 (d, J = 12 Hz, 1H, SCHH), 3.68 (d, J = 12 Hz, 1H, SCHH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 195.8, 149.0, 147.8, 140.5, 135.3, 132.3, 128.9, 128.5, 125.6, 122.9, 100.2, 46.4, 42.4.



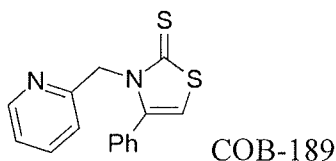
[0249] COB-153 was prepared from COB-152 according to Synthetic Example 3. Based on 23.4 mg of product recovered, the yield was 90%. For the COB-153, the following data were obtained: Was prepared from COB-152 following the general procedure to afford 23.4 mg (90%). R_f 0.46 (60% EtOAc in hexanes); t_R = 9.25 min; ^1H NMR (CDCl $_3$, 300 MHz) δ 8.38 (dd, J = 1.5, 4.8 Hz, 1H, Py), 7.94 (d, J = 1.6 Hz, 1H, Py), 7.43-7.29 (m, 4H, Ph), 7.10-7.03 (m, 3H, Ph, Py), 6.43 (s, 1H, CH), 5.36 (s, 2H, PyCH $_2$); ^{13}C NMR (CDCl $_3$, 75 MHz) δ 189.4, 149.2, 148.9, 144.5, 135.5, 131.4, 130.5, 130.45, 129.6, 129.2, 123.6, 109.3, 48.5.



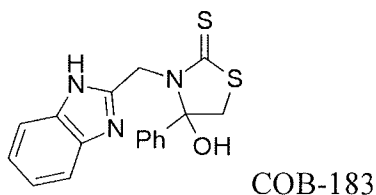
[0250] COB-176 was prepared according to Synthetic Example 2 on a 1.5-mmol scale. Based on 104 mg of product recovered, the yield was 23%. For the COB-176, the following data were obtained: R_f 0.23 (10 % MeOH in EtOAc); t_R = 2.76 min; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, J = 2 Hz, 1H, Ar), 8.53 (dd, J = 1.5, 5 Hz, 1H, Ar), 8.28 (d, J = 1.5 Hz, 1H, Ar), 8.00 (dd, J = 1.3, 4.8 Hz, 1H, Ar), 7.77-7.20 (m, 2H, Ar), 7.28 (dd, J = 4.8, 7.9 Hz, 1H, Ar), 7.19 (s, 1H), 7.03 (dd, J = 4.9, 7.8 Hz, 1H, Ar), 5.7 (d, J = 14.9 Hz, 1H, NCHH), 4.26 (d, J = 14.9 Hz, 1H, NCHH), 3.74 (d, J = 12.2 Hz, 1H, SCHH), 3.54 (d, J = 12.2 Hz, 1H, SCHH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.9, 150.4, 149.0, 147.6, 147.3, 138.3, 136.7, 134.0, 133.6, 123.9, 123.8, 100.0, 47.0, 43.5.



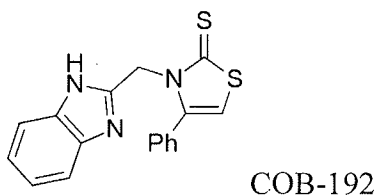
[0251] COB-180 was prepared according to Synthetic Example 2 on a 1.88-mmol scale. Based on 300 mg of product recovered, the yield was 84%. For the COB-180, the following data were obtained: R_f 0.34 (20 % EtOAc in hexanes); t_R = 10.8 min; ^1H NMR ($DMSO-d_6$, 300 MHz) δ 8.42 (d, J = 4.8 Hz, 1H, Ar), 8.27 (s, 1H, OH), 7.75-7.70 (m, 1H, Ar), 7.51-7.48 (m, 2H, Ar), 7.42-7.21 (m, 5H, Ar), 4.95 (d, J = 16.2 Hz, 1H, NCHH), 4.38 (d, J = 16.2 Hz, 1H, NCHH), 3.79 (d, J = 12.1 Hz, 1H, SCHH), 3.71 (d, J = 12.1 Hz, 1H, SCHH); ^{13}C NMR ($DMSO-d_6$, 75 MHz) δ 196.6, 155.2, 148.1, 140.8, 136.7, 128.8, 128.6, 125.8, 122.2, 122.1, 99.8, 50.7, 43.1.



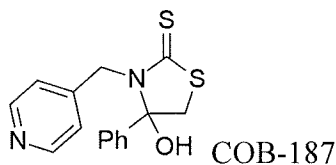
[0252] COB-189 was prepared from COB-180 according to Synthetic Example 3 on a 0.5-mmol scale. Based on 129.4 mg of product recovered, the yield was 91%. For the COB-189, the following data were obtained: R_f 0.16 (20 % EtOAc in hexanes); t_R = 6.05 min; ^1H NMR (CDCl_3 , 300 MHz) δ 8.460-8.39 (m, 1H, Ar), 7.56-7.50 (m, 1H, Ar), 7.35-6.98 (m, 7H, Ar), 6.47 (s, 1H, CH), 5.37 (s, 2H, NCH_2); ^{13}C NMR (CDCl_3 , 75 MHz) δ 189.2, 155.0, 149.7, 145.4, 136.7, 130.8, 130.1, 129.6, 129.0, 122.5, 121.7, 52.8.



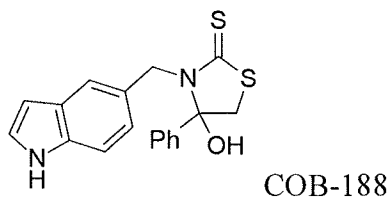
[0253] COB-183 was prepared according to Synthetic Example 2 on a 1.88-mmol scale. Based on 214 mg of product recovered, the yield was 50%. For the COB-183, the following data were obtained: R_f 0.16 (20% EtOAc in hexanes); t_R = 12.28 min; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 12.39 (s, 1H, NH), 8.76 (s, 1H, OH), 7.61-7.37 (m, 7H, Ar), 7.18-7.16 (m, 2H, Ar), 5.18 (d, J = 16.5 Hz, 1H, NCHH), 4.40 (d, J = 16.5 Hz, 1H, NCHH), 3.80 (d, J = 12 Hz, 1H, SCHH), 3.70 (d, J = 12 Hz, 1H, SCHH); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 198.2, 150.0, 140.5, 129.0, 128.6, 126.1, 121.9, 99.7, 43.9, 43.5.



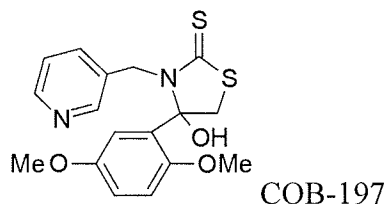
[0254] COB-192 was prepared from COB-183 according to Synthetic Example 3 on a 0.07-mmol scale. Based on 13 mg of product recovered, the yield was 63%. For the COB-192, the following data were obtained: R_f 0.4 (5% EtOAc in toluene); t_R = 6.95 min; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 12.4 (s, 1H, NH), 7.58-7.55 (m, 3H, Ar), 7.45-7.38 (m, 4H, Ar), 7.16-7.11 (m, 3H, Ar and SCH), 5.41 (s, 2H, NCH_2); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 188.0, 148.9, 144.5, 142.9, 134.1, 130.4, 129.8, 129.2, 128.7, 122.1, 121.2, 118.6, 111.2, 109.6, 45.7.



[0255] COB-187 was prepared according to Synthetic Example 2 on a 1.88-mmol scale. Based on 70 mg of product recovered, the yield was 20%. For the COB-187, the following data were obtained: R_f 0.3 (10 % EtOAc in toluene); t_R = 8.59 min; ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.39-8.37 (d, 2H, Ar), 7.84 (s, 1H, OH), 7.39-7.35 (m, 5H, Ar), 7.16-7.15 (m, 2H, Ar), 4.80 (d, J = 16.1 Hz, 1H, NCHH), 4.51 (d, J = 16.1 Hz, 1H, NCHH), 3.78 (d, J = 12.1 Hz, 1H, SCHH), 3.71 (d, J = 12.1 Hz, 1H, SCHH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 196.0, 148.9, 145.6, 140.5, 128.9, 128.5, 125.6, 122.3, 100.1, 47.8, 42.4.

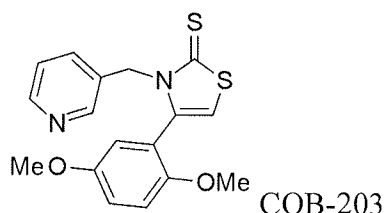


[0256] COB-188 was prepared according to Synthetic Example 2 on a 1.88-mmol scale. Based on 107 mg of product recovered, the yield was 25%. For the COB-188, the following data were obtained: R_f 0.25 (10% EtOAc in toluene); t_R = 14.41 min; ^1H NMR (CDCl₃, 300 MHz) δ 8.91 (s, 1H, NH), 7.45-7.35 (m, 5H, Ph), 7.31-7.14 (m, 5H, Ar), 6.47 (s, 1H, OH), 5.82 (d, J = 14.5 Hz, 1H, NCHH), 4.21 (d, J = 14.5 Hz, 1H, NCHH), 3.61 (d, J = 12.1 Hz, 1H, SCHH), 3.38 (d, J = 12.1 Hz, 1H, SCHH); ^{13}C NMR (CDCl₃, 75 MHz) δ 198.4, 139.6, 135.4, 129.3, 128.9, 127.9, 127.8, 126.2, 124.9, 122.8, 121.2, 111.5, 102.9, 100.8, 49.6, 44.0.

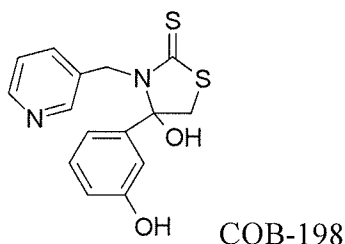


[0257] COB-197 was prepared according to Synthetic Example 2 on a 3-mmol scale. Based on 450 mg of product recovered, the yield was 62%. For the COB-197, the following data were obtained: R_f 0.4 (60 % EtOAc in hexanes); t_R = 5.33 min; ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.27-8.25 (m, 1H, Ar), 8.09 (d, 1H, Ar), 7.87 (s, 1H, OH), 7.42 (d, 1H, Ar), 7.25 (d, 1H, Ar), 7.11-7.07 (m, 1H, Ar), 6.80-6.77 (m, 1H, Ar), 6.50 (d, 1H, Ar), 4.91 (d, J = 15.3 Hz, 1H, NCHH), 4.38 (d, J = 15.3 Hz, 1H, NCHH), 3.85 (d, J = 12 Hz, 1H, SCHH), 3.72 (s, 3F1,

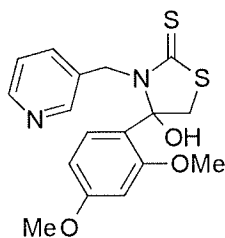
OCH₃), the signal corresponding to the second MeO overlaps with the water peak, 3.28 (d, J = 12 Hz, 1H, SCHH); ¹³C NMR (DMSO-d₆, 75 MHz) δ 194.4, 150.7, 148.1, 147.1, 145.6, 133.5, 130.3, 126.3, 120.5, 113.2, 111.3, 109.9, 95.4, 53.6, 53.4 43.8.



[0258] COB-203 was prepared from COB-197 according to Synthetic Example 3 on a 0.27-mmol scale. Based on 84 mg of product recovered, the yield was 90%. For the COB-203, the following data were obtained: R_f 0.32 (60% EtOAc in hexanes); t_R = 4.13 min (LCMS); ¹H NMR (CDCl₃, 300 MHz) δ 8.33 (d, 1H, Ar), 7.91 (s, 1H, Ar), 7.41 (d, 1H, Ar), 7.08-7.04 (m, 1H, Ar), 6.93-6.89 (in, 1H, Ar), 6.79 (d, 1H, Ar), 6.39-6.38 (m, 2H, Ar and CH), 5.26 (s, 2H, CH₂), 3.58 (s, 3H, OMe), 3.22 (s, 3H, OMe).

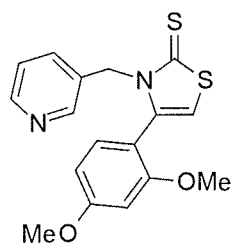


[0259] COB-198 was prepared according to Synthetic Example 2 on a 1.5-mmol scale. Based on 69.9 mg of product recovered, the yield was 22%. For the COB-198, the following data were obtained: R_f 0.3 (60% EtOAc in hexanes); t_R = 5.49 min; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.37-8.35 (m, 2H, Ar and ArOH), 7.82 (s, 1H, OH), 7.63-7.60 (m, 1H, Ar), 7.27-7.13 (m, 3H, Ar), 6.82-6.71 (m, 3H, Ar), 4.85 (d, J = 15.3 Hz, 1H, NCHH), 4.43 (d, J = 15.3 Hz, 1H, NCHH), the SCH₂ peaks overlap with the water peak. The compound was not pure after three purifications according to HPLC (89% purity).



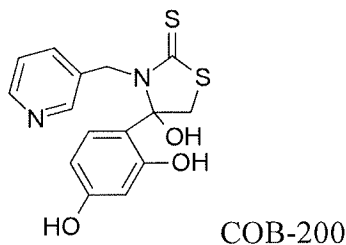
COB-199

[0260] COB-199 was prepared according to Synthetic Example 2 on a 1.5-mmol scale. Based on 203 mg of product recovered, the yield was 56%. For the COB-199, the following data were obtained: R_f 0.3 (60% EtOAc in hexanes); t_R = 3.39 min (LCMS); ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.25 (dd, 1H, Ar), 8.07 (d, 1H, Ar), 7.73 (s, 1H, OH), 7.56 (d, 1H, Ar), 7.40 (dt, 1H, Ar), 7.12-7.07 (m, 1H, Ar), 6.53 (dd, 1H, Ar), 6.08 (d, 1H, Ar), 4.91 (d, J = 15.3 Hz, 1H, NCHH), 4.31 (d, J = 15.3 Hz, 1H, NCHH), 3.83 (d, J = 12 Hz, 1H, SCHH), 3.71 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.25 (d, J = 12 Hz, 1H, SCHH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 196.0, 161.5, 157.1, 135.4, 132.4, 122.3, 119.9, 109.9, 97.6, 55.3, 40.3.

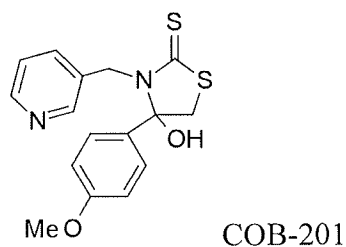


COB-204

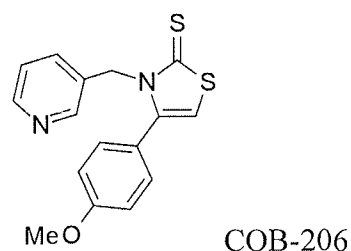
[0261] COB-204 was prepared from COB-199 according to Synthetic Example 3 on a 0.28-mmol scale. Based on 81 mg of product recovered, the yield was 87%. For the COB-204, the following data were obtained: R_f 0.32 (60% EtOAc in hexanes); t_R = 4.03 min (LCMS); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, 1H, Ar), 7.99 (s, 1H, Ar), 7.53 (d, 1H, Ar), 7.28-7.11 (m, 1H, Ar), 6.85 (d, 1H, Ar), 6.456.41 (m, 3H, Ar and CH), 5.29 (s, 2H, CH_2), 3.82 (s, 3H, OMe), 3.59 (s, 3H, OMe).



[0262] COB-200 was prepared according to Synthetic Example 2 on a 1.5-mmol scale. Based on 131 mg of product recovered, the yield was 40%. For the COB-200, the following data were obtained: R_f 0.11 (60% EtOAc in hexanes); t_R = 2.75 min (LCMS); ^1H and ^{13}C NMR were not optimal, but based on the LCMS (96.9%), the compound was considered clean enough to be sent for tests.

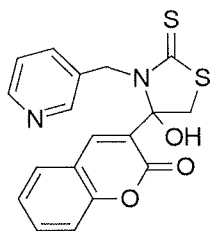


[0263] COB-201 was prepared according to Synthetic Example 2 on a 1.6-mmol scale. Based on 153 mg of product recovered, the yield was 46%. For the COB-201, the following data were obtained: R_f 0.28 (60% EtOAc in hexanes); t_R = 3.56 min (LCMS); ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.36-8.35 (m, 2H, Ar), 7.75 (s, 1H, OH), 7.58 (d, 1H, Ar), 7.32-7.21 (m, 3H, Ar), 6.89 (d, 2H, Ar), 4.77 (d, J = 15.4 Hz, 1H, NCHH), 4.52 (d, J = 15.4 Hz, 1H, NCHH), 3.373.68 (m, 5H, SCH_2 and OCH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 195.6, 159.5, 148.9, 147.7, 135.3, 132.4, 132.35, 127.0, 122.8, 113.7, 100.1, 55.2, 46.9, 42.5.



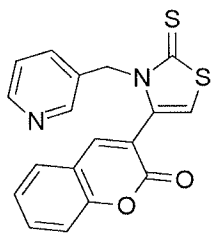
[0264] COB-206 was prepared from COB-201 according to Synthetic Example 3 on a 0.18-mmol scale. Based on 39 mg of product recovered, the yield was 69%. For the COB-206, the following data were obtained: R_f 0.26 (60% EtOAc in hexanes); t_R = 4.15 min (LCMS); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, 1H, Ar), 8.0 (s, 1H, Ar), 7.43 (d, 1H, Ar),

7.13-7.08 (m, 1H, Ar), 6.95 (d, 2H, Ar), 6.82 (d, 2H, Ar), 6.39 (s, 1H, CH), 5.35 (s, 2H, CH₂), 3.76 (s, 3H, OMe).



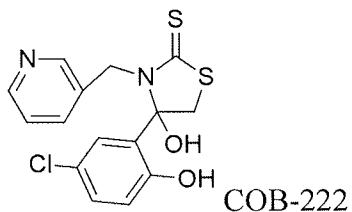
COB-202

[0265] COB-202 was prepared according to Synthetic Example 2 on a 1.5-mmol scale. Based on 114 mg of product recovered, the yield was 35%. For the COB-202, the following data were obtained: R_f 0.22 (60% EtOAc in hexanes); t_R = 3.12 min (LCMS); ¹H NMR (DMSO-d₆, 300 MHz) δ 8.41 (s, 1H, OH), 8.28-8.23 (m, 3H, Ar), 7.87 (dd, 1H, Ar), 7.66-7.56 (m, 2H, Ar), 7.41-7.36 (td, 1H, Ar), 7.28 (d, 1H, Ar), 7.08 (dd, 1H, CH), 5.08 (d, J = 15.5 Hz, 1H, NCHH), 4.56 (d, J = 15.5 Hz, 1H, NCHH), 3.98 (d, J = 12.3 Hz, 1H, SCHH), 3.28 (d, J = 12.3 Hz, 1H, SCHH) this signal overlaps with the signal for water; ¹³C NMR was recorded, but the signal was weak such that only six carbon are observed.

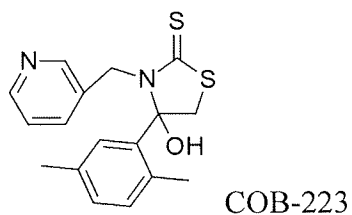


COB-205

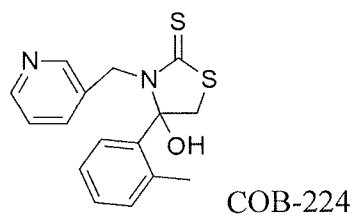
[0266] COB-205 was prepared from COB-202 according to Synthetic Example 3 on a 0.13-mmol scale. Based on 33.4 mg of product recovered, the yield was 70%. For the COB-205, the following data were obtained: R_f 0.25 (60% EtOAc in hexanes); t_R = 3.46 min (LCMS); ¹H NMR (CDCl₃, 300 MHz) δ 8.34 (s, 1H, Ar), 8.20 (s, 1H, Ar), 7.59-7.43 (m, 2H, Ar), 7.34 (s, 1H, Ar), 7.33-7.30 (m, 2H, Ar), 7.25-7.06 (m, 1H, Ar), 6.59 (s, 1H, CH), 5.51 (s, 2H, CH₂).



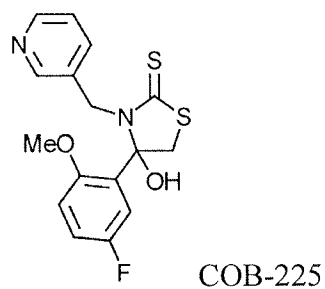
[0267] COB-222 may be prepared according to Synthetic Example 2.



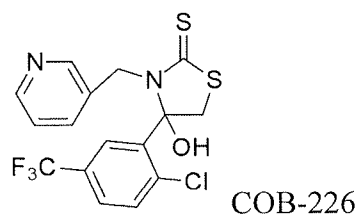
[0268] COB-223 may be prepared according to Synthetic Example 2.



[0269] COB-224 may be prepared according to Synthetic Example 2.



[0270] COB-225 may be prepared according to Synthetic Example 2.



[0271] COB-226 may be prepared according to Synthetic Example 2.

Example 4 – Characterizations of COB-152 and COB-187 and GSK-3 Inhibition:

Characterization of GSK-3 Inhibition by Fluorescence-Based Molecular Assay

[0272] *Materials and Methods.* Compounds of General Formula (I) and (II) were identified as highly potent inhibitors of GSK-3, revealed by a molecular assay. The ability of two compounds from the series of compounds of General Formula (I) and (II), particularly COB-152 and COB-187, to inhibit the activity of GSK-3 α and GSK-3 β , was determined in a fluorescence-based molecular assay.

[0273] To conduct the fluorescence-based molecular assay, the compounds COB-152 and COB-187 were mixed with GSK-3 α or GSK-3 β in the presence of a Ser/Thr substrate and ATP. The level of compound was varied, and the reaction was carried out for 60 minutes at room temperature. Subsequently, the solution was developed and the fluorescence was read to infer the activity of the protein.

[0274] *Results.* As shown in FIGS 1A, 1B, 2A, and 2B, COB-152 and COB-187 inhibit the activity of GSK-3 α/β . FIG 1A shows the effect of COB-152 on GSK-3 α activity; FIG 1B shows the effect of COB-152 on GSK-3 β activity; FIG 2A shows the effect of COB-187 on GSK-3 α activity; and FIG. 2B shows the effect of COB-187 on GSK-3 β activity. The results clearly revealed that both COB-152 and COB-187 inhibit the activity of both GSK-3 α and GSK-3 β . The IC₅₀ for each compound was in the nanomolar range.

Example 5 – Characterizations of COB-152 and COB-187 and GSK-3 Inhibition:

Kinase Screening

[0275] *Materials and Methods.* The imidazole and/or thiazole compounds (*i.e.*, I-GSK-3s) had limited effect on non-GSK-3 kinases in a molecular assay. To gain insight into the specificity of compounds for GSK-3, an extensive kinase screen was employed, in which COB-152 was screened against 315 additional kinases at a 2 μ M concentration and COB-187 was screened against select kinases at a 1 μ M concentration.

[0276] *Results.* As shown in TABLE 3 provided below, such analysis revealed that less than 5% of the non-GSK-3 kinases were inhibited at greater than 20%. Only 2 of the non-GSK-3 kinases were inhibited above 35%, and these were inhibited, on average, by only 47%. In contrast, GSK-3 α and GSK-3 β were inhibited, on average, by 83%. Because GSK-3

inhibitors often affect cyclin-dependent protein kinases (CDKs), it is striking that the I- GSK-3 compounds had limited to no effect on the CDKs. The results with the CDKs along with GSK-3 are given in FIG. 3. As shown in FIG. 3, COB-152 and COB-187 inhibit the activity of GSK-3 α/β while having little effect on non-GSK-3 kinases, such as the cyclin dependent protein kinases.

TABLE 3: % Kinase Inhibition by COB-152 and COB-187

Legend

< 70% Inhibition
$\geq$ 70% Inhibition *

Compound	COB-152	COB-187
Concentration (nM)	2000	1000
Kinase		
ABL1	-2	
ABL1 E255K	3	6
ABL1 G250E	1	
ABL1 T315I	2	
ABL1 Y253F	5	
ABL2 (Arg)	1	
ACVR1 (ALK2)	8	
ACVR1B (ALK4)	4	
ACVR2B	31	
ADRBK1 (GRK2)	6	
ADRBK2 (GRK3)	8	
AKT1 (PKB alpha)	0	
AKT2 (PKB beta)	9	0
AKT3 (PKB gamma)	7	3
AMPK A1/B1/G1	14	
AMPK A2/B1/G1	16	
AURKA (Aurora A)	17	5
AURKB (Aurora B)	-5	
AURKC (Aurora C)	10	
AXL	19	
BLK	-6	
BMPR1A (ALK3)	10	
BMX	0	

BRAF	14	
BRAF	15	
BRAF V599E	18	
BRAF V599E	15	
BRSK1 (SAD1)	12	0
BTK	6	
CAMK1 (CaMK1)	1	5
CAMK1D (CaMKI delta)	19	
CAMK2A (CaMKII alpha)	14	
CAMK2B (CaMKII beta)	9	17
CAMK2D (CaMKII delta)	13	4
CAMK4 (CaMKIV)	17	
CAMKK1 (CAMKKA)	7	
CAMKK2 (CaMKK beta)	25	
CDC42 BPA (MRCKA)	-4	
CDC42 BPB (MRCKB)	4	
CDK1/cyclin B	3	
CDK2/cyclin A	-7	
CDK5/p25	2	
CDK5/p35	7	3
CDK7/cyclin H/MNAT1	2	
CDK8/cyclin C	11	
CDK9/cyclin K	4	
CDK9/cyclin T1	-8	
CHEK1 (CHK1)	-6	
CHEK2 (CHK2)	6	
CHUK (IKK alpha)	3	
CLK1	3	
CLK2	6	
CLK3	4	
CLK4	17	
CSF1R (FMS)	3	1
CSK	5	
CSNK1A1 (CK1 alpha 1)	4	
CSNK1D (CK1 delta)	3	
CSNK1E (CK1 epsilon)	6	
CSNK1G1 (CK1 gamma 1)	-5	
CSNK1G2 (CK1 gamma 2)	5	
CSNK1G3 (CK1 gamma 3)	13	
CSNK2A1 (CK2 alpha 1)	4	
CSNK2A2 (CK2 alpha 2)	6	
DAPK1	-4	
DAPK3 (ZIPK)	2	

DCAMKL2 (DCK2)	2	
DDR1	-4	
DDR2	3	
DMPK	11	
DNA-PK	5	
DYRK1A	3	
DYRK1B	9	
DYRK3	6	1
DYRK4	2	
EEF2K	3	
EGFR (ErbB1)	-1	
EGFR (ErbB1) L858R	1	
EGFR (ErbB1) L861Q	-2	
EGFR (ErbB1) T790M	-2	
EGFR (ErbB1) T790M L858R	4	3
EPHA1	9	
EPHA2	1	
EPHA3	13	
EPHA4	23	
EPHA5	2	
EPHA7	6	
EPHA8	10	
EPHB1	2	
EPHB2	6	
EPHB3	18	
EPHB4	5	
ERBB2 (HER2)	-7	
ERBB4 (HER4)	2	
FER	-2	-4
FES (FPS)	0	
FGFR1	-1	
FGFR2	4	
FGFR3	3	
FGFR3 K650E	3	
FGFR4	4	
FGR	27	9
FLT1 (VEGFR1)	5	
FLT3	-5	
FLT3 D835Y	7	8
FLT4 (VEGFR3)	18	
FRAP1 (mTOR)	-4	
FRK (PTK5)	6	
FYN	8	

GRK4	19	18
GRK5	0	
GRK6	11	
GRK7	2	
GSG2 (Haspin)	-4	
GSK3A (GSK3 alpha) *	80*	89*
GSK3B (GSK3 beta) *	74*	90*
HCK	8	
HIPK1 (Myak)	2	
HIPK2	1	
HIPK3 (YAK1)	7	
HIPK4	6	
IGF1R	4	
IKBKB (IKK beta)	11	1
IKBKE (IKK epsilon)	4	0
INSR	-2	
INSRR (IRR)	7	
IRAK1	4	
IRAK4	-3	
ITK	0	
JAK1	0	
JAK2	7	
JAK2 JH1 JH2	-2	
JAK2 JH1 JH2 V617F	-2	
JAK3	12	7
KDR (VEGFR2)	64	11
KIT	-6	
KIT T670I	7	
KIT V654A	2	
LCK	4	
LIMK1	7	
LIMK2	1	
LRRK2	-15	
LRRK2 G2019S	9	
LTK (TYK1)	6	
LYN A	5	
LYN B	1	
MAP2K1 (MEK1)	16	
MAP2K1 (MEK1)	15	
MAP2K1 (MEK1) S218D S222D	29	
MAP2K2 (MEK2)	27	
MAP2K2 (MEK2)	18	
MAP2K3 (MEK3)	22	

MAP2K6 (MKK6)	29	
MAP2K6 (MKK6)	15	
MAP2K6 (MKK6) S207E T211E	22	
MAP3K10 (MLK2)	5	
MAP3K11 (MLK3)	4	
MAP3K14 (NIK)	17	
MAP3K2 (MEKK2)	1	
MAP3K3 (MEKK3)	5	
MAP3K5 (ASK1)	-2	
MAP3K7/MAP3K7IP1 (TAK1-TAB1)	21	
MAP3K8 (COT)	18	
MAP3K9 (MLK1)	1	
MAP4K2 (GCK)	7	7
MAP4K4 (HGK)	6	12
MAP4K5 (KHS1)	26	
MAPK1 (ERK2)	5	
MAPK10 (JNK3)	26	
MAPK10 (JNK3)	6	
MAPK11 (p38 beta)	7	
MAPK12 (p38 gamma)	6	
MAPK13 (p38 delta)	5	
MAPK14 (p38 alpha)	27	17
MAPK14 (p38 alpha) Direct	3	
MAPK3 (ERK1)	5	
MAPK8 (JNK1)	22	
MAPK8 (JNK1)	1	
MAPK9 (JNK2)	20	
MAPK9 (JNK2)	-1	
MAPKAPK2	2	5
MAPKAPK3	14	7
MAPKAPK5 (PRAK)	57	55
MARK1 (MARK)	4	
MARK2	7	
MARK3	6	
MARK4	6	
MATK (HYL)	0	
MELK	15	4
MERTK (cMER)	1	
MET (cMet)	14	
MET M1250T	2	
MINK1	12	6
MKNK1 (MNK1)	6	
MKNK2 (MNK2)	7	

MLCK (MLCK2)	26	
MST1R (RON)	7	
MST4	9	
MUSK	10	
MYLK (MLCK)	6	
MYLK2 (skMLCK)	6	
NEK1	23	0
NEK2	7	
NEK4	1	
NEK6	14	
NEK7	-1	
NEK9	0	
NLK	39	
NTRK1 (TRKA)	8	
NTRK2 (TRKB)	-2	
NTRK3 (TRKC)	11	
NUAK1 (ARK5)	-8	
PAK1	6	
PAK2 (PAK65)	8	
PAK3	8	
PAK4	13	
PAK6	17	
PAK7 (KIAA1264)	1	
PASK	2	-5
PDGFRA (PDGFR alpha)	2	
PDGFRA D842V	5	
PDGFRA T674I	1	
PDGFRA V561D	3	
PDGFRB (PDGFR beta)	6	
PDK1	12	
PDK1 Direct	11	
PHKG1	13	
PHKG2	3	
PI4KA (PI4K alpha)	6	
PI4KB (PI4K beta)	-2	
PIK3C2A (PI3K-C2 alpha)	11	
PIK3C2B (PI3K-C2 beta)	2	
PIK3C3 (hVPS34)	18	
PIK3CA/PIK3R1 (p110 alpha/p85 alpha)	2	
PIK3CD/PIK3R1 (p110 delta/p85 alpha)	-14	-5
PIK3CG (p110 gamma)	6	

PIM1	-3	
PIM2	15	
PKN1 (PRK1)	2	
PLK1	12	
PLK2	15	
PLK3	10	9
PRKACA (PKA)	-1	-3
PRKCA (PKC alpha)	4	-4
PRKCB1 (PKC beta I)	1	
PRKCB2 (PKC beta II)	12	3
PRKCD (PKC delta)	11	
PRKCE (PKC epsilon)	0	
PRKCG (PKC gamma)	4	12
PRKCH (PKC eta)	8	1
PRKCI (PKC iota)	7	
PRKCN (PKD3)	10	
PRKCQ (PKC theta)	11	-8
PRKCZ (PKC zeta)	14	
PRKD1 (PKC mu)	17	
PRKD2 (PKD2)	17	
PRKG1	4	3
PRKG2 (PKG2)	2	
PRKX	8	1
PTK2 (FAK)	7	
PTK2B (FAK2)	5	
PTK6 (Brk)	-3	
RAF1 (cRAF) Y340D Y341D	10	
RAF1 (cRAF) Y340D Y341D	10	
RET	8	
RET V804L	2	
RET Y791F	4	
RIPK2	0	
ROCK1	1	
ROCK2	1	6
ROS1	5	
RPS6KA1 (RSK1)	4	
RPS6KA2 (RSK3)	6	
RPS6KA3 (RSK2)	11	5
RPS6KA4 (MSK2)	6	
RPS6KA5 (MSK1)	7	
RPS6KA6 (RSK4)	21	8
RPS6KB1 (p70S6K)	10	
SGK (SGK1)	12	7

SGK2	15	2
SGKL (SGK3)	11	4
SLK	9	
SNF1LK2	6	
SPHK1	17	20
SPHK2	9	
SRC	-1	
SRC N1	6	
SRMS (Srm)	22	
SRPK1	5	
SRPK2	0	
STK16 (PKL12)	-10	
STK17A (DRAK1)	31	
STK22B (TSSK2)	9	
STK22D (TSSK1)	5	
STK23 (MSSK1)	5	
STK24 (MST3)	9	
STK25 (YSK1)	12	
STK3 (MST2)	3	
STK33	-4	
STK4 (MST1)	1	
SYK	2	
TAOK2 (TAO1)	3	
TAOK3 (JIK)	8	
TBK1	6	
TEC	14	
TEK (Tie2)	2	
TGFBR1 (ALK5)	10	
TNK2 (ACK)	11	
TTK	22	
TXK	5	
TYK2	3	
TYRO3 (RSE)	11	
WEE1	13	
WNK2	10	
YES1	10	
ZAK	33	
ZAP70	-5	

Example 6 – Treatment of Murine and Human Macrophages with COB-152 and COB-187

[0277] *Materials.* COB-152 and COB-187 were obtained from Dr. Stephen Bergmeier at Ohio University (Athens, OH). Dulbecco's modified Eagle's medium (*i.e.*, DMEM) and fetal bovine serum (*i.e.*, FBS) were obtained from Thermo Scientific (Waltham, MA), whereas a penicillin-streptomycin stabilized solution was obtained from Lonza (Basel, Switzerland).

[0278] *Western Blotting.* Micro BCA Protein Assay kit was obtained from Thermo Scientific (Rockford, IL). Nu-PAGE 4 to 12% Bis-Tris denaturing gels, nitrocellulose membrane (0.2 μ m), running and transfer buffers, sample reducing agent, loading buffer, and antioxidant were purchased from Invitrogen (Carlsbad, CA). Bovine Serum Albumin (*i.e.*, BSA) and 10X PBS were obtained from Sigma Aldrich and Gibco, respectively. IRDye (680/800) protein marker, IRDye 800 CW conjugated secondary donkey anti-goat IgG and IRDye 680 CW conjugated donkey anti-rabbit IgG, and stripping buffer were purchased from LI-COR Biosciences (Lincoln, NE). Rabbit monoclonal anti-human total GSK-3 and rabbit polyclonal anti-human β -catenin antibodies were obtained from Cell Signaling Technology (Danvers, MA).

[0279] *Primers for Quantitative RT-PCR.* RNeasy plus mini kit and Qiashredder columns were obtained from Qiagen (Valencia, CA). High capacity cDNA Reverse Transcription Kit, Taqman Gene Expression Master Mix, primer for endogenous control HPRT1 (assay id: HS99999909_m1), and IL-6 primer (assay id: Hs00985639_m1) were obtained from Applied Biosystems (Foster City, CA). Mouse β -catenin (assay id: Mm99999915_g1) and mouse glyceraldehyde 3-phosphate dehydrogenase (*i.e.*, GAPDH) endogenous control (Assay id: Mm99999915_g1) were obtained from Applied Biosystems (Waltham, MA).

[0280] *Cell Culture.* RAW 264.7 cells were cultured in RPMI 1640 medium supplemented with 10% FBS and 0.5% penicillin-streptomycin stabilized solution. THP-1 cells were cultured and differentiated into macrophages using phorbol 12-myristate 13-acetate (*i.e.*, PMA). More specifically, THP-1 cells were cultured in RPMI-1640 10% FBS supplemented with 0.05 mM 2-mercaptoethanol. For differentiation to a macrophage phenotype, THP-1 cells were stimulated with PMA (50 ng/mL) for 24 hours. Differentiated THP-1 cells were washed with fresh media twice before incubation for 24 more hours at 37 °C, 5% CO₂ in a humidified incubator. The monolayer was then treated with ox-LDL or native LDL (both at either 50 or

100 µg/mL) and LPS (10 ng/mL) for 4 hours. Undifferentiated THP-1 cells were cultured and treated under similar conditions were used as a control.

[0281] *Methods. Detection of GSK-3 and β -catenin by Western Blotting.* There is substantial evidence that GSK-3 inhibition leads to an increased expression of β -catenin, and this unique property of GSK-3 can be utilized to identify specific GSK-3 inhibitors. To test the ability of COB-187 and COB-152 to increase β -catenin levels, RAW 264.7 macrophages and PMA differentiated THP-1 cells were treated with COB-152 or COB 187 at different concentrations or 0.1% (v/v) DMSO solvent for 5 hours. Following treatment, protein was extracted and probed for β -catenin and total GSK-3 via western blotting.

[0282] More specifically, RAW 264.7 cells and PMA differentiated THP-1 cells were treated with varying concentrations of COB-187 or COB-152 dissolved in culture media containing 0.1% (v/v) dimethylsulfoxide (*i.e.*, DMSO) solvent or with 0.1% (v/v) DMSO alone for 5 or 24 hours. After incubation, 20 µg protein was extracted from the cells and quantified. More specifically, culture supernatant was collected and store at -80 °C until further use. The cells were lysed in 10 mM Tris HCl at pH 7.5, 150 mM NaCl, and 1% nonyl phenoxypolyethoxylethanol-40, containing a cocktail of protease inhibitors (Roche, Mannheim, Germany). Insoluble material was pelleted and the supernatant containing total protein as well as the culture supernatant was quantified using a Micro BCA protein kit. 20 µg of protein was then resolved onto a denaturing gel, transferred to a nitrocellulose membrane, and immunoblotted with antibodies against GSK-3 and β -catenin. Signals were detected using the Li-Cor Odyssey Infrared Imaging System (Lincoln, NE). Membranes were stripped and reprobed with primary antibody for β -actin as a loading control. All experiments were performed at least thrice in both RAW 264.7 and PMA differentiated THP-1 cells, and in duplicates.

[0283] *Detection of β -Catenin by Quantitative RT-PCR.* RAW 264.7 cells were treated with varying concentrations of COB-187, COB-152 or 0.1% (v/v) DMSO solvent alone for 5 or 24 hours. Following treatment, RNA was extracted from the cells and reverse transcribed. More specifically, total RNA was isolated using RNeasy plus mini kit according to the manufacturer's protocol and quantified using a Nanodrop 2000C Spectrophotometer. First-strand cDNA was synthesized from total RNA using cDNA Reverse Transcription Kit according to the manufacturer's protocol. Quantitative RT-PCR was performed using Taqman Gene Expression Assay (Life Technologies, Waltham, MA) and mouse primers for GAPDH

and β -catenin. Relative gene expression was determined by normalizing with GAPDH using the comparative Ct method. All experiments were performed at least thrice in duplicates.

[0284] *Results.* Treatment with COB-152 and COB-187 Increases β -catenin Protein Expression in Murine and Human Macrophages. As shown in FIGS. 4A-4B, treatment with COB-152 and COB-187 resulted in increased expression of β -catenin protein in RAW 264.7 murine macrophages, which was clearly evident at concentrations of COB-152 and COB-187 $\geq 10 \mu\text{M}$. Such expression increased in a dose-dependent manner upon treatment with COB-152 and COB-187. Additionally, it was noted that expression of GSK-3 may also be affected at higher concentrations of COB-152 and COB-187, such as, e.g., $10 \mu\text{M}$ and $25 \mu\text{M}$. Without being bound by the theory, it is believed that in addition to inhibition of GSK-3 activity, COB-152 and COB-187 may also have an effect on the overall expression of GSK-3.

[0285] As shown in FIGS. 5A-5B, treatment with COB-152 and COB-187 resulted in increased expression of β -catenin protein in PMA differentiated THP-1 cells, which was clearly evident at concentrations of COB-152 and COB-187 $\geq 10 \mu\text{M}$. Additionally, it was noted that expression of GSK-3 may also be affected at higher concentrations of COB-152 and COB-187, such as, e.g., $10 \mu\text{M}$ and $25 \mu\text{M}$. Without being bound by the theory, it is believed that in addition to inhibition of GSK-3 activity, COB-152 and COB-187 may also have an effect on the overall expression of GSK-3.

[0286] Moreover, as shown in FIGS. 6A-6B, treatment with COB-152 and COB-187 did not alter expression of β -catenin mRNA in macrophages in RAW 264.7 murine macrophages. Without being bound by the theory, it is believed that COB-152 and COB-187 inhibit GSK-3 activity at the post-transcriptional level.

Example 7 – Effect of COB-152 and COB-187 on Amyloid- β - and LPS-Induced Inflammatory Cytokines

[0287] *Materials.* Human A β (1-42) peptides were purchased from U.S. Peptide Inc. (Rancho, Cucamonga, CA). Primers for quantitative RT-PCR were purchased from Applied Biosystems. Mouse IL-6 primers (Assay id: Mm00446190_m1) and GAPDH endogenous control (Assay id: Mm99999915_g1) were obtained from Applied Biosystems. Human IL-6 (Assay id: Hs00985639_m1), TNF- α (Assay id: Hs00985639_m1), IL-1 α (Assay id:

Hs00174092_m1), IL-1 β (Assay id: Hs01555410_m1), IFN- β (Assay id: Hs01077958_s1), and HPRT1 (Assay id: Hs01003267_m1) primers were all purchased from Applied Biosystems.

[0288] *Methods. LPS Stimulation of RAW 264.7 and THP-1 Cells.* RAW 264.7 were stimulated with either LPS (10 ng/mL) alone, or in combination with COB-152, COB-187 or 0.1% DMSO solvent for 5 hours. Following incubation, RNA was extracted from the cells. Quantitative RT-PCR was used to quantify expression of mRNA.

[0289] *A β Stimulation of Differentiated THP-1 Cells.* In order to obtain an optimal cytokine induction without cell death, different concentrations of A β (1-42) peptides were tested at different times. To do so, THP-1 cells were differentiated using PMA (50 ng/mL) as previously described. These differentiated THP-1 cells were stimulated with A β (1-42) peptides at concentrations ranging from 1 μ M to 50 μ M for 5 and 24 hours.

[0290] *LPS and A β Stimulation of Human Macrophages.* THP-1 cells were differentiated using PMA (50 ng/mL) as previously described and stimulated with either LPS (10 ng/mL) or 10 μ M human A β (1-42) peptides alone, or in combination with COB-152, COB-187 or 0.1% DMSO solvent for 5 hours. Following incubation, the supernatant was collected and stored at -80 °C until assayed for IL-6, TNF- α , and IL-1 β protein by ELISA, whereas RNA extracted from the cells was reverse transcribed and subjected to quantitative RT-PCR for quantification of IL-6, TNF- α , IL-1 α , IL-1 β , and IFN- β mRNA. All experiments were performed at least thrice and in duplicates.

[0291] *Quantitative RT-PCR and Cytokine ELISA.* RNA extracted from differentiated THP-1 cells treated as previously described was reverse transcribed to cDNA and subjected to quantitative RT-PCR. Relative IL-6, TNF- α , IL-1 α , IL-1 β , and IFN- β gene expression was determined by normalizing with Hprt1 using the comparative Ct method. Commercially available cytokine ELISA kits (BD Biosciences, Burlington, NC) were used to quantify the levels of secreted IL-6, TNF- α , and IL-1 β protein in the supernatant obtained from differentiated THP-1 cells treated with either LPS (10 ng/mL) or 10 μ M human A β (1-42) peptides alone, or in combination with COB-152, COB-187 or 0.1% DMSO solvent. The ELISA was performed according to the manufacturer's protocol. The supernatant was diluted with the assay diluent at different ratios as shown in the **TABLE 4** below for IL-6, TNF- α , and IL-1 β . All samples were tested in duplicates and the results were expressed as Mean $\pm$ SD of the cytokine concentration (pg/mL). All results presented were corrected for dilution factor.

TABLE 4: Culture Supernatant Dilutions for Cytokine ELISA

Stimulant	Supernatant Dilutions		
	IL-6	TNF- α	IL-1 β
A β	1:3	1:20	1:33
LPS	1:5	1:40	1:33

[0292] *Statistics and Data Analysis.* Data for differentiated THP-1 cells stimulated with LPS or A β (1-42) peptides alone, or in combination with COB-152, COB-187, or 0.1% DMSO solvent are given as Mean $\pm$ SD of three independent experiments.

[0293] *Results. COB-152 Modulates TLR-4 Signaling by Attenuating IL-6 Production in Murine Macrophages.* As shown in FIG. 7, COB-152 inhibits IL-6 expression in LPS induced RAW macrophages. More specifically, COB-152 dose dependently inhibited IL-6 mRNA production in LPS stimulated murine macrophages. IL-6 expression was measured and normalized to GAPDH/HPRT1 mRNA levels, by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0294] *A β Peptides Induce the Production of Inflammatory Cytokines in a Concentration-Dependent Manner.* As shown in FIGS. 8A-8D, there was a concentration-dependent increase in mRNA expression of IL-6, TNF- α , IL-1 α , and IL-1 β in PMA differentiated THP-1 cells stimulated with A β (1-42) peptides at concentrations ranging from 1 μ M to 50 μ M for 5 and 24 hours. A maximum induction was observed at 25 μ M. Such effect was more pronounced at 5 hours compared to 24 hours. Cytokine expression was measured, and normalized to HPRT1 mRNA levels, by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0295] *COB-152 and COB-187 Modulate A β -Induced Inflammatory Cytokine Production in Human Macrophages.* As shown in FIGS. 9A-9D and 10A-10D, there was a dose-dependent decrease in IL-6 and TNF- α production in PMA differentiated THP-1 human macrophages stimulated with A β (1-42) peptides (10 μ M) in the presence of COB-152 or COB-187. Secreted IL-6 protein levels (FIGS. 9B and 9D) and TNF- α protein levels (FIGS. 10B and 10D) were determined by ELISA, whereas IL-6 mRNA levels (FIGS. 9A and 9C) and TNF- α mRNA levels (FIGS. 10A and 10C) were measured and normalized to HPRT1 mRNA levels by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0296] As shown in FIGS. **11A-11B**, COB-152 decreased IL-1 β protein production in PMA differentiated THP-1 human macrophages stimulated with A β (1-42) peptides (10 μ M) at a concentration of ≥ 25 μ M. As shown in FIGS. **11C-11D**, COB-187 decreased IL-1 β protein production in PMA differentiated THP-1 human macrophages stimulated with A β (1-42) peptides (10 μ M) at a concentration of ≥ 10 μ M. Secreted IL-1 β protein levels (FIGS. **11B** and **11D**) were determined by ELISA, whereas IL-1 β mRNA (FIGS. **11A-11C**) were measured and normalized to HPRT1 mRNA levels by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0297] As shown in FIGS. **12A-12B** and **13A-13B**, COB-152 and COB-187 inhibited IL-1 α and IFN- β mRNA expression in PMA differentiated THP-1 human macrophages stimulated with A β (1-42) peptides (10 μ M). More specifically, COB-152 and COB-187 inhibited IL-1 α and IFN- β mRNA expression in PMA differentiated THP-1 human macrophages stimulated with A β (1-42) peptides (10 μ M) in a dose-dependent manner. IL-1 α and IFN- β mRNA were measured and normalized to HPRT1 mRNA levels by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0298] *COB-152 and COB-187 Modulate LPS-Induced Inflammatory Cytokine Production in Human Macrophages.* As shown in FIGS. **14A-14D** and **15A-15D**, there was a dose-dependent decrease in IL-6 and TNF- α production in PMA differentiated THP-1 human macrophages stimulated with LPS (10 ng/mL) in the presence of COB-152 or COB-187. Secreted IL-6 protein levels (FIGS. **14B** and **14D**) and TNF- α protein levels (FIGS. **15B** and **15D**) were determined by ELISA, whereas IL-6 mRNA levels (FIGS. **14A** and **14C**) and TNF- α mRNA levels (FIGS. **15A** and **15C**) were measured and normalized to HPRT1 mRNA levels by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0299] As shown in FIG. **16D**, there was a dose-dependent decrease in IL-1 β protein production in PMA differentiated THP-1 human macrophages stimulated with LPS (10 ng/mL) in the presence of COB-187. As shown in FIG. **16B**, there was a decrease in IL-1 β protein production in PMA differentiated THP-1 human macrophages stimulated with LPS (10 ng/mL) in the presence of COB-152 at a concentration of ≥ 50 μ M. IL- β protein levels (FIGS. **16B** and **16D**) were determined by ELISA, whereas IL- β mRNA levels (FIGS. **16A** and **16C**) were measured and normalized to HPRT1 mRNA levels by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

[0300] As shown in FIGS. 17A-17B, COB-152 and COB-187 inhibited IL-1 α mRNA expression in PMA differentiated THP-1 human macrophages stimulated with LPS (10 ng/mL). IL-1 α mRNA was measured and normalized to HPRT1 mRNA levels by quantitative RT-PCR. Data values represent Mean $\pm$ SD.

Example 8 – Characterizations of COB-152 and GSK-3 Inhibition: Inhibition of TLR-4 Induced Signaling Products

[0301] Materials and Methods. The imidazole and/or thiazole compounds (*i.e.*, I-GSK-3s) inhibited products of TLR-4 induced signaling. Another known hallmark of GSK-3 inhibition is suppression of immune products (*e.g.*, cytokines) induced by Toll like receptor (TLR) signaling.

[0302] Results. It was observed that the I-GSK-3 compounds inhibited products of TLR signaling. For example, the I-GSK-3 compound COB-152 were found to inhibit lipopolysaccharide (*i.e.*, LPS) induction of reactive products (*e.g.*, iNOS) in murine macrophages with an IC₅₀ of about 160 nM. LPS is a known trigger of TLR-4 signaling. Additionally, such inhibition did not appear to be due to cell death, as the concentration of COB-152 required to kill 50% of the murine macrophages, *i.e.*, the TC₅₀, was over 100 greater than the IC₅₀. As shown in FIG. 18, COB-152 inhibited LPS (a known ligand for TLR-4) induction of iNOS transcripts. The IC₅₀ for COB-152 was determined to be about 160 nM. The ratio of the TC₅₀ to IC₅₀ for COB-152 exceeded 100. The samples of FIG. 8 included an untreated sample; LPS — treated with LPS alone; DMSO — treated with LPS and DMSO (carrier control); 0.1 μ M COB-152 — treated with LPS and 0.1 μ M COB-152; 1 μ M COB-152 — treated with LPS and 1 μ M COB-152; and 10 μ M COB-152 — treated with LPS and 10 μ M COB-152.

Example 9 – Preparation of Pharmaceutical Compositions: Composition Administration

[0303] Means of administering active compounds according to embodiments herein include, but are not limited to, oral, sublingual, intravenous, intramuscular, intraperitoneal, percutaneous, intranasal, intrathecal, subcutaneous, or enteral. Local administration to the afflicted site may be accomplished through means known in the art, including, but not limited

to, topical application, injection, infusion and implantation of a porous device in which the active compound(s) or compositions described herein are contained. Accordingly, the active compounds described herein will generally be administered as a pharmaceutical composition comprising one or more active compounds described herein in combination with a pharmaceutically acceptable excipient and other formulational aids.

Example 10 – Preparation of Pharmaceutical Compositions: Formulational Aids

[0304] Such compositions may be aqueous solutions, emulsions, creams, ointments, suspensions, gels, liposomal suspensions, and the like. Suitable excipients include water, saline, Ringer's solution, dextrose solution, and solutions of ethanol, glucose, sucrose, dextran, mannose, mannitol, sorbitol, polyethylene glycol (PEG), phosphate, acetate, gelatin, collagen, Carbopol®, vegetable oils, and the like. One may additionally include suitable preservatives, stabilizers, antioxidants, antimicrobials, and buffering agents, for example, BHA, BHT, citric acid, ascorbic acid, tetracycline, and the like. Cream or ointment bases useful in formulation include lanolin, Silvadene® (Marion), Aquaphor® (Duke Laboratories), and the like. Alternatively, one may incorporate or encapsulate the active compounds described herein in a suitable polymer matrix or membrane, thus providing a sustained-release device suitable for implantation near the site to be treated locally. Other devices include indwelling catheters and devices such as the Alzet® minipump. Ophthalmic preparations may be formulated using commercially available vehicles such as Sorbi-care® (Allergan), Neodecdron® (Merck, Sharp & Dohme), Lacrilube®, and the like. Further, one may provide the active compounds described herein in bulking agents, for example human serum albumin, sucrose, mannitol, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in Remington's Pharmaceutical Sciences I (Mack Pub. Co.), incorporated herein by reference.

Example 11 – Preparation of Pharmaceutical Compositions: Oral/Parenteral Administration

[0305] The active compounds and pharmaceutical compositions according to embodiments herein can be administered both orally and parenterally in accordance with conventional procedures for the treatment of autoimmune disease and performance of organ and/or tissue transplantation. The amount of active compound required to treat any particular autoimmune

and/or transplant disorder will, of course, vary depending upon the nature and severity of the disorder, the age and condition of the subject, and other factors readily determined by one of ordinary skill in the art. Active compounds are administered in dosage units, preferably divided dosage units, containing the active compound with a suitable physiologically acceptable carrier or excipient, many of which are well known to those in the art and are described above. The dosage units can be in the form of a liquid preparation, e.g., solutions, suspensions, dispersions, or emulsions, or they may be in solid form such as pills, tablets, capsules or the like. Compositions in unit dosage form, i.e., pharmaceutical compositions which are available in a pre-measured form suitable for single dose administration without requiring that the individual dosage be measured out by the user, for example, pills, tablets, capsules, or ampoules are particularly preferred methods of administration of the active compounds described herein.

Example 12 - Preparation of Pharmaceutical Compositions: Specific/Preferred Indications

[0306] Pharmaceutical compositions in dosage unit form may include an amount of composition which provides from about 0.05 mg to about 60 mg, preferably from about 0.05 mg to about 20 mg, of active compound per day. To produce dosage units for peroral administration, the active compound according to embodiments herein or a salt thereof is combined, e.g., with solid powdered carriers such as lactose, sucrose, mannitol; starches such as potato starch, corn starch or amylopectin, as well as laminaria powder and citrus pulp powder; cellulose derivatives of gelatin, also lubricants such as magnesium or calcium stearate of polyethylene glycols (carbowaxes) of suitable molecular weights may be added, to form compressed tablets or core tablets for sugar coating. The latter are coated, for example, with concentrated sugar solutions which, e.g., can contain gum arabic, talcum and/or titanium dioxide, or they are coated with a lacquer dissolved in easily volatile organic solvents or mixture of organic solvents. Dyestuffs can be added to these coatings, for example, to distinguish between different contents of active substance. Capsules useful herein include, for example, soft gelatin capsules (pearl-shaped closed capsules), gels, other capsules which consist, for example, of a mixture of gelatin and glycerin and contain, e.g., mixtures of the active substances or a suitable salt thereof with solid, powdered carriers such as, e.g., lactose, sucrose, sorbitol, mannitol; starches such as potato starch corn starch or amylopectin, cellulose

derivatives or gelatin, as well as magnesium stearate or steric acid. Suppositories are employed as dosage units for rectal application. These consist of a combination of the active substance or a suitable salt thereof with a neutral fatty base, or also gelatin rectal capsules can be employed which consist of a combination of the active substance or a suitable salt thereof with polyethylene glycols (carbowaxes) of suitable molecular weight.

[0307] Ampoules for parenteral administration, particularly intramuscular administration, preferably contain an active compound or a water soluble salt thereof and suitable stabilizing agents, and, if necessary, buffer substances in aqueous solution. Anti-oxidizing agents such as sodium bisulfite, sodium sulfite, ascorbic acid or Rongalit (formaldehyde-sodium bisulfite compound), and the like are suitable as stabilizing agents either alone or combined, in total concentrations from about 0.01% to about 0.05% by weight of the composition. Because of its ability to form chelates, ascorbic acid has an additional stabilizing effect; in this function it can also be replaced by other chelate-formers. The best suitability of the active ingredient is attained, e.g., by mixtures in suitable ratio of sodium sulfite, sodium bisulfite and/or ascorbic acid, or by the addition of other buffer substances such as citric acid and/or salts thereof. In addition, the ampoules can contain a slight amount of a preservative.

[0308] Useful pharmaceutical formulations for administration of the active compounds according to embodiments herein may be illustrated below. They are made using conventional techniques.

[0309] CAPSULES

[0310] Active ingredient 0.05 to 20 mg

[0311] Lactose 20-100 mg

[0312] Corn Starch U.S.P. 20-100 mg

[0313] Aerosolized silica gel 2-4 mg

[0314] Magnesium stearate 1-2 mg

[0315] TABLETS

[0316] Active ingredient 0.05 to 20 mg

[0317] Microcrystalline cellulose 50 mg

[0318] Corn Starch U.S.P. 80 mg

- [0319] Lactose U.S.P. 50 mg
- [0320] Magnesium stearate U.S.P. 1-2 mg
- [0321] The tablets can be sugar coated according to conventional art practices. Colors may be added to the coating.
- [0322] CHEWABLE TABLETS
- [0323] Active ingredient 0.05 to 20 mg
- [0324] Mannitol, N.F. 100 mg
- [0325] Flavor 1 mg
- [0326] Magnesium stearate U.S.P. 2 mg
- [0327] SUPPOSITORIES
- [0328] Active ingredient 0.05 to 20 mg
- [0329] Suppository base 1900 mg
- [0330] LIQUID
- [0331] Active ingredient 2.0 percent
- [0332] Polyethylene glycol 300, N.F. 10.0 percent
- [0333] Glycerin 5.0 percent
- [0334] Sodium bisulfite 0.02 percent
- [0335] Sorbitol solution 70%, U.S.P. 50 percent
- [0336] Methylparaben, U.S.P. 0.1 percent
- [0337] Propylparaben, U.S.P. 0.2 percent
- [0338] Distilled water, U.S.P. (q.s.) 100.0 cc
- [0339] INJECTABLE
- [0340] Active ingredient 0.05 to 60 mg
- [0341] Polyethylene glycol 600 1.0 cc
- [0342] Sodium bisulfite, U.S.P. 0.4 mg
- [0343] Water for injection, U.S.P. (q.s.) 2.0 cc

[0344] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the claimed subject matter belongs. The terminology used in the description herein is for describing particular embodiments only and is not intended to be limiting. As used in the specification and appended claims, the singular forms “a,” “an,” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. For example, reference to “a cell” may include both reference to a single cell and reference to a plurality of cells.

[0345] It is noted that terms like “preferably,” “commonly,” and “typically” are not utilized herein to limit the scope of the appended claims or to imply that certain features are critical, essential, or even important to the structure or function of the claimed subject matter. Rather, these terms are merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment.

[0346] It is to be further understood that where descriptions of various embodiments use the term “comprising,” and/or “including” those skilled in the art would understand that in some specific instances, an embodiment can be alternatively described using language “consisting essentially of” or “consisting of.”

[0347] For the purposes of describing and defining the present disclosure it is noted that the term “substantially” is utilized herein to represent the inherent degree of uncertainty that may be attributed to any quantitative comparison, value, measurement, or other representation. The term “substantially” is also utilized herein to represent the degree by which a quantitative representation may vary from a stated reference without resulting in a change in the basic function of the subject matter at issue.

[0348] All documents cited are incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present disclosure.

[0349] While particular embodiments of the present disclosure have been illustrated and described, it would be obvious to one skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the disclosure. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this disclosure.

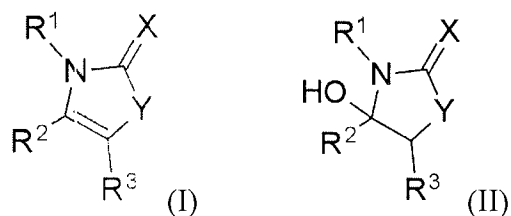
[0350] It should be understood that every maximum numerical limitation given throughout this specification includes every lower numerical limitation, as if such lower numerical limitations were expressly written herein. Every minimum numerical limitation given throughout this specification will include every higher numerical limitation, as if such higher numerical limitations were expressly written herein. Every numerical range given throughout this specification will include every narrower numerical range that falls within such broader numerical range, as if such narrower numerical ranges were all expressly written herein.

[0351] Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers and optical and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

CLAIMS

1. A method for modulating glycogen synthase kinase-3 (GSK-3) activity in a cell expressing GSK-3, the method comprising:

contacting the cell with a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which:

R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin;

R^3 is chosen from $-\text{H}$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

X is S or O; and

Y is S or NH;

with the proviso that when R^2 is phenyl and R^3 is $-\text{H}$, at least one of the following is true:

- (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof;
- (b) R^1 is hexyl;
- (c) R^1 is $\text{Ph}(\text{CH}_2)_n-$, where n is 2 or 3; or

- (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

2. The method of claim 1, wherein the contacting is effective to modulate the activity of at least one of GSK-3 α or GSK-3 β in the cell.
3. The method of claim 1, wherein the activity of GSK-3 is modulated by inhibiting the GSK-3 activity.
4. The method of claim 1, wherein the activity of GSK-3 is modulated by inhibiting the GSK-3 activity by at least about 50%.
5. The method of claim 1, wherein the activity of GSK-3 is modulated by inhibiting the GSK-3 activity by at least about 75%.
6. The method of claim 1, wherein the at least one compound of General Formula (I) or (II) is provided in a concentration of from about 1 nM to about 50 μ M.
7. The method of claim 1, wherein:
the activity of GSK-3 is modulated by inhibiting the GSK-3 activity, and
the at least one compound of General Formula (I) or (II) has an IC_{50} value of from about 100 pM to about 50 μ M.
8. The method of claim 1, wherein the at least one compound of General Formula (I) or (II) is specific for GSK-3.

9. The method of claim 1, wherein the contacting is effective to modulate signaling of GSK-3.
10. The method of claim 1, wherein the contacting is effective to enhance expression of β -catenin.
11. The method of claim 1, wherein the contacting is effective to inhibit function of lipopolysaccharide (LPS).
12. The method of claim 1, wherein the contacting is effective to suppress expression of at least one of i-Nitrous-Oxide Synthase (iNOS), Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α), Interleukin 1 β (IL-1 β), Interleukin 1 α (IL-1 α), Interferon β (IFN- β), or Interferon γ (IFN- γ).
13. The method of claim 1, wherein the contacting is effected *in vitro*.
14. The method of claim 1, wherein the contacting is effected *in vivo*.
15. The method of claim 1, wherein the activity of GSK-3 is a phosphorylation activity.
16. The method of claim 1, wherein the cell is a mammalian cell.
17. The method of claim 1, wherein the at least one compound of General Formula (I) or (II) is a thiazole 2-thione.
18. The method of claim 1, wherein:
R³ is -H;
X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

19. The method of claim 1, wherein:

R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R^3 is $-H$;

X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

20. The method of claim 1, wherein:

R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N;

R^3 is $-H$;

X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

21. The method of claim 1, wherein:

R^1 is chosen from C_1 to C_4 aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N;

R^3 is $-H$;

X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

22. The method of claim 1, wherein:

R^1 is chosen from C_1 to C_4 aliphatic groups optionally substituted with heteroaryl groups in which one or more ring atoms is N, or combination thereof;

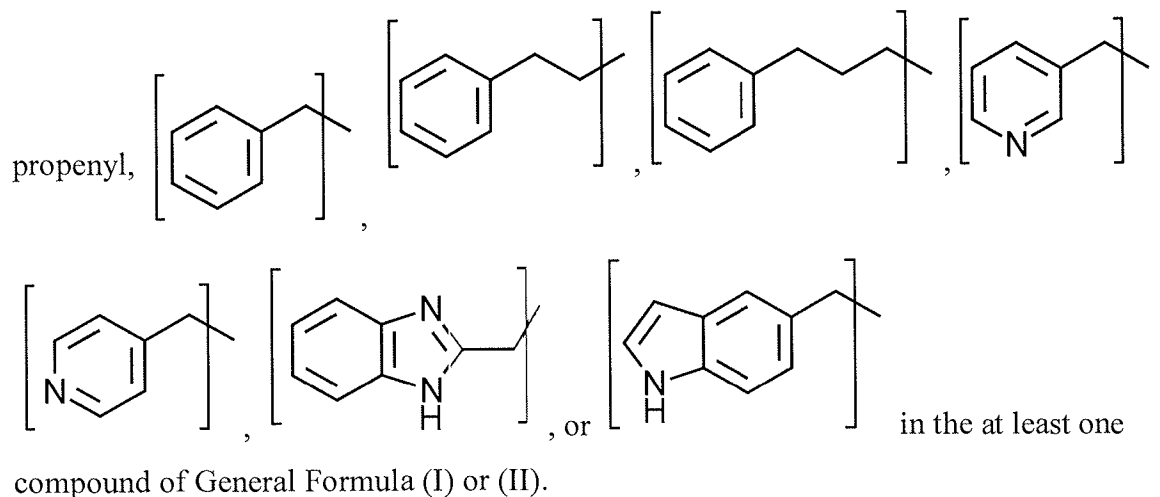
R^2 is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N;

R^3 is -H;

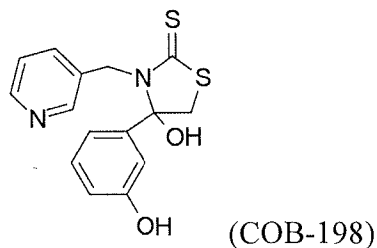
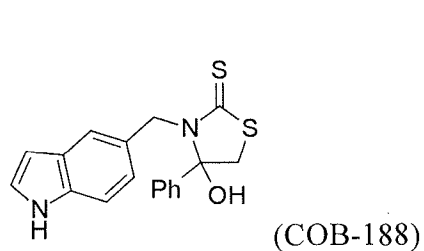
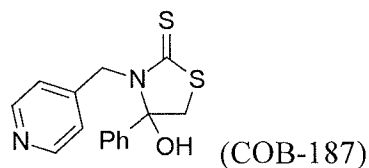
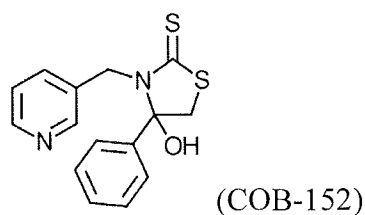
X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

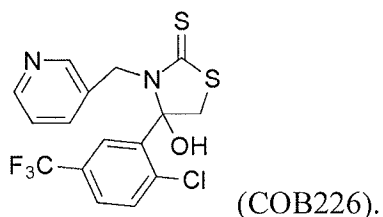
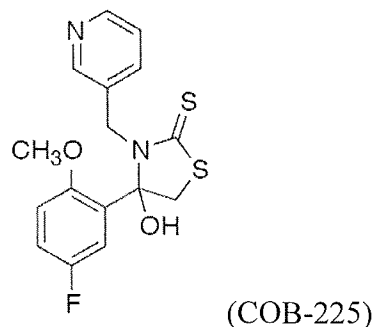
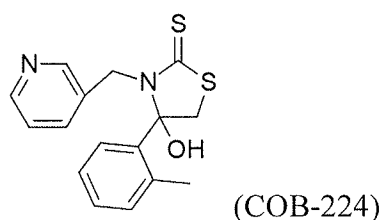
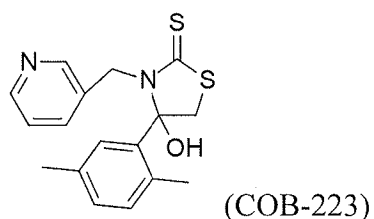
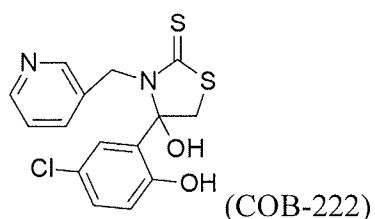
23. The method of claim 1, wherein R^1 is chosen from methyl, ethyl, propyl, butyl, 2-



24. The method of claim 1, wherein the at least one compound of General Formula (I) or (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:

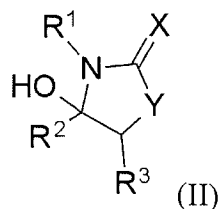
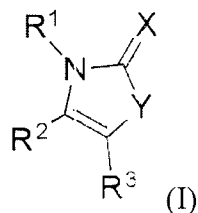


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25. A method for modulating glycogen synthase kinase-3 (GSK-3) signaling, the method comprising:

contacting a cell expressing GSK-3 with a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which:

R¹ is chosen from C₁ to C₁₀ aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin;

R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

X is S or O; and

Y is S or NH;

with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true:

- (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof;
- (b) R^1 is hexyl;
- (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or
- (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

26. The method of claim 25, wherein the contacting is effective to enhance expression of β -catenin, inhibit function of lipopolysaccharide (LPS), or suppress expression of i-Nitrous-Oxide Synthase (iNOS), Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α), Interleukin 1 β (IL-1 β), Interleukin 1 α (IL-1 α), Interferon β (IFN- β), or Interferon γ (IFN- γ).

27. The method of claim 25, wherein the at least one compound of General Formula (I) or (II) is a thiazole 2-thione.

28. The method of claim 25, wherein:

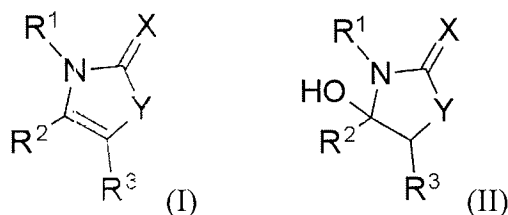
R^3 is $-H$;

X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

29. A method for treating a GSK-3-mediated disorder in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of at least one compound of General Formula (I) or (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which:

R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin;

R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

X is S or O; and

Y is S or NH;

with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true:

- (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof;
- (b) R^1 is hexyl;
- (c) R^1 is $\text{Ph}(\text{CH}_2)_n$, where n is 2 or 3; or
- (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

30. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from malaria, cancer, insulin resistance, type 2 diabetes mellitus, muscle wasting, neurodegenerative disease, cardiovascular disease, myocardial disease, pathological inflammation, bone disease, renal disease, human immunodeficiency virus (HIV)-related neurological disorder, sepsis, toxic shock, psychiatric disease, central nervous system (CNS) disease, or combination thereof.

31. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from leukemia, pancreatic cancer, multiple myeloma, glioblastoma, or combination thereof.

32. The method of claim 29, wherein the GSK-3 mediated disorder is acute lymphoblastic leukemia (ALL).

33. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis (ALS), or combination thereof.

34. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from atherosclerosis, cardiac ischemia, cardiac reperfusion injury, cardiac hypertrophy, or combination thereof.

35. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from sepsis, toxic shock, or combination thereof.
36. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from parenchymal renal disease, proliferative renal disease, or combination thereof.
37. The method of claim 29, wherein the GSK-3 mediated disorder is neuroAIDS.
38. The method of claim 29, wherein the GSK-3 mediated disorder is chosen from bipolar disorder, mood disorder, schizophrenia, depression, or combination thereof.
39. The method of claim 29, wherein the at least one compound of General Formula (I) or (II) is a thiazole 2-thione.
40. The method of claim 29, wherein:
R³ is -H;
X is S; and
Y is S in the at least one compound of General Formula (I) or (II).
41. The method of claim 29, wherein:
R¹ is chosen from C₁ to C₄ aliphatic or heteroaliphatic groups optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;
R² is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N;
R³ is -H;
X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

42. The method of claim 29, wherein:

R¹ is chosen from C₁ to C₄ aliphatic groups optionally substituted with heteroaryl groups in which one or more ring atoms is N, or combination thereof;

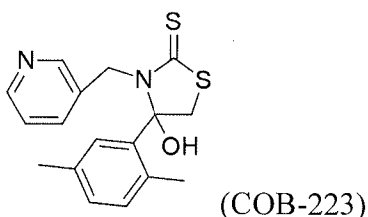
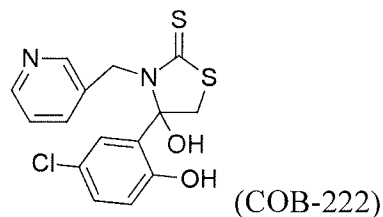
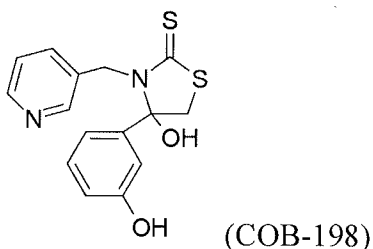
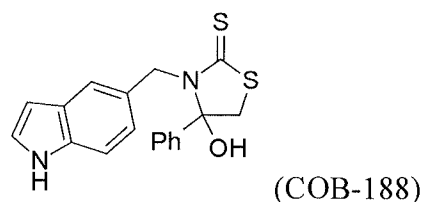
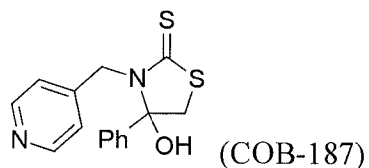
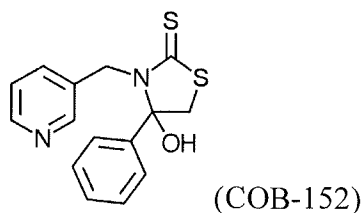
R² is chosen from unsubstituted phenyl groups, substituted phenyl groups, or heteroaryl groups in which one or more ring atoms is N;

R³ is -H;

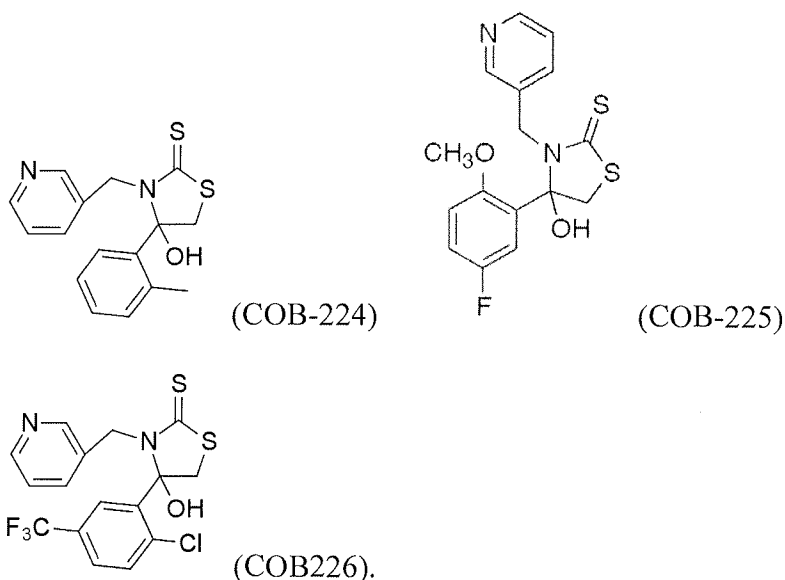
X is S; and

Y is S in the at least one compound of General Formula (I) or (II).

43. The method of claim 29, wherein the at least one compound of General Formula (I) or (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:



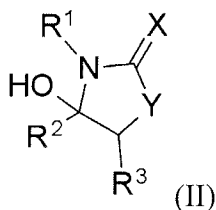
125



44. The method of claim 29, wherein the administering comprises administering a pharmaceutical composition comprising the at least one compound of General Formula (I) or (II) in combination with at least one pharmaceutically-acceptable carrier.

45. A method for modulating glycogen synthase kinase-3 (GSK-3) activity in a cell expressing GSK-3, the method comprising:

contacting the cell with a therapeutically effective amount of at least one compound of General Formula (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which:

R¹ is chosen from C₁ to C₁₀ aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R² is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin;

R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

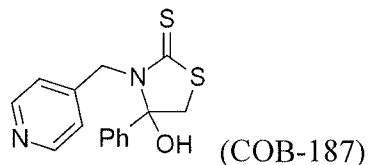
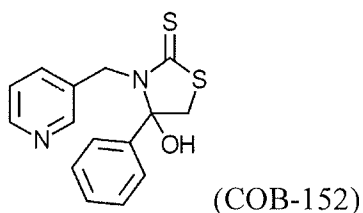
X is S or O; and

Y is S or NH;

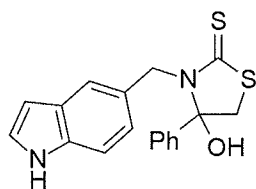
with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true:

- (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof;
- (b) R^1 is hexyl;
- (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or
- (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

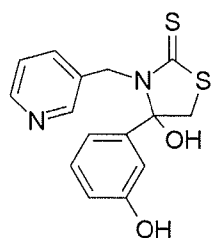
46. The method of claim 45, wherein the at least one compound of General Formula (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:



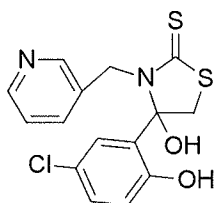
127



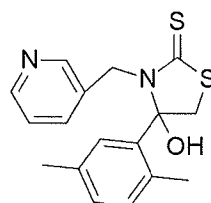
(COB-188)



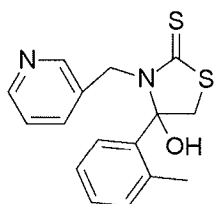
(COB-198)



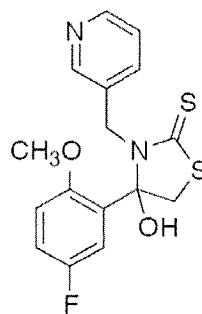
(COB-222)



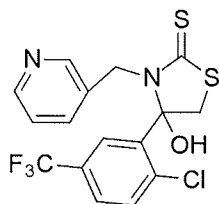
(COB-223)



(COB-224)



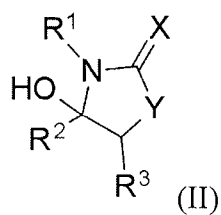
(COB-225)



(COB-226).

47. A method for inhibiting glycogen synthase kinase-3 (GSK-3) activity in a cell expressing GSK-3, the method comprising:

contacting the cell with a therapeutically effective amount of at least one compound of General Formula (II):



or a pharmaceutically-acceptable salt or solvate thereof, in which:

R^1 is chosen from C_1 to C_{10} aliphatic or heteroaliphatic groups, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

R^2 is chosen from aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, and coumarin;

R^3 is chosen from $-H$, C_1 to C_{10} aliphatic or heteroaliphatic groups, phenyl, or substituted phenyl, wherein the aliphatic or heteroaliphatic groups are optionally substituted with one or more phenyl groups, aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof;

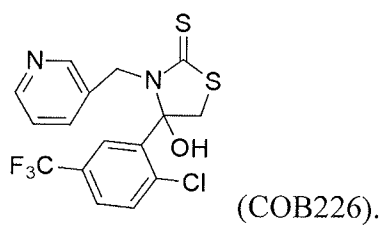
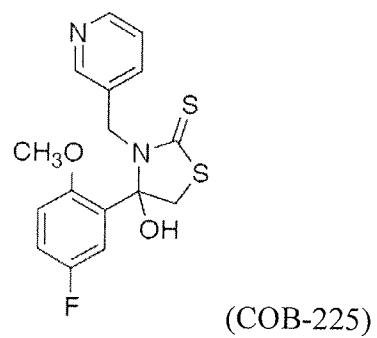
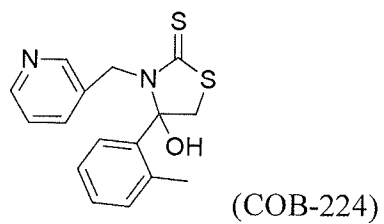
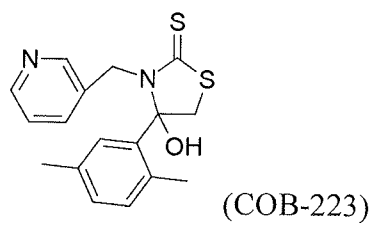
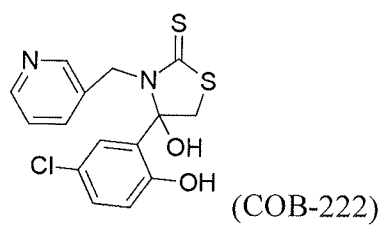
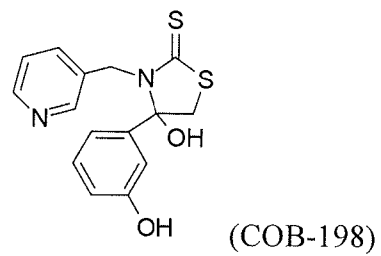
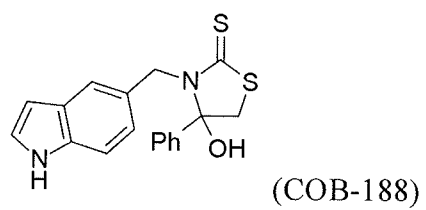
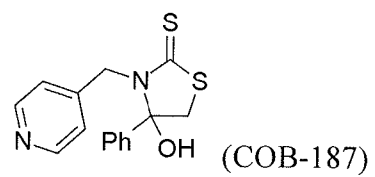
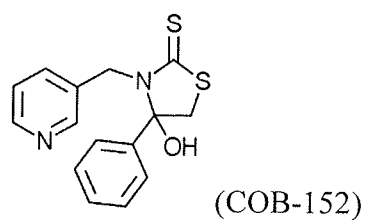
X is S or O; and

Y is S or NH;

with the proviso that when R^2 is phenyl and R^3 is $-H$, at least one of the following is true:

- (a) R^1 is a C_1 to C_{10} aliphatic or heteroaliphatic group that is substituted with at least one substituted aryl group, at least one heteroaryl group, at least one substituted heteroaryl group, or combination thereof;
- (b) R^1 is hexyl;
- (c) R^1 is $Ph(CH_2)_n-$, where n is 2 or 3; or
- (d) R^1 is a C_1 to C_{10} heteroaliphatic group, optionally substituted with one or more aryl groups, substituted aryl groups, heteroaryl groups, substituted heteroaryl groups, or combination thereof.

48. The method of claim 47, wherein the at least one compound of General Formula (II) is chosen from COB-152, COB-187, COB-188, COB-198, COB-222, COB-223, COB-224, COB-225, COB-226, or combination thereof, and pharmaceutically acceptable salts and solvates thereof:



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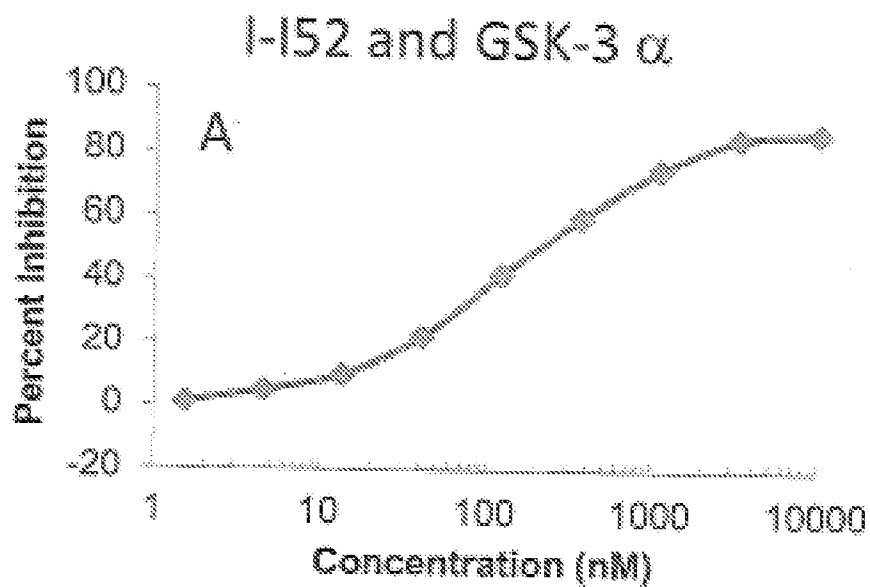


FIG. 1A

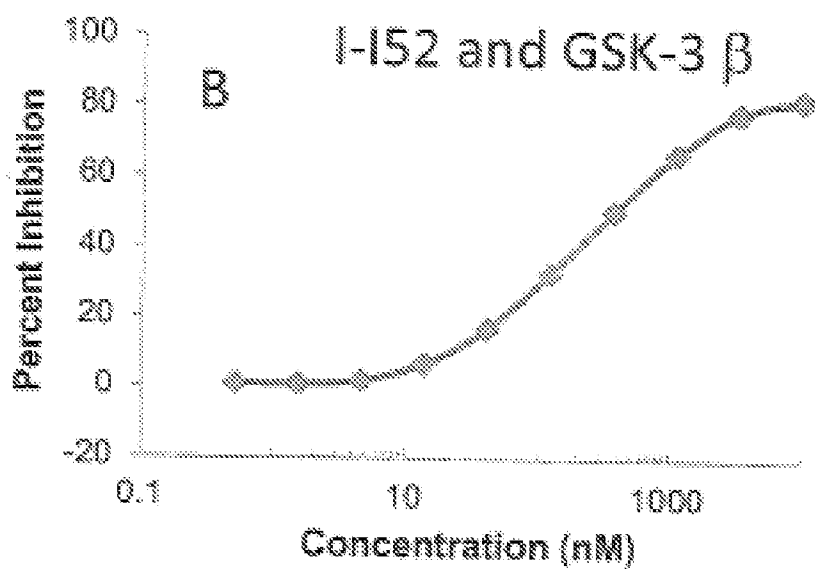


FIG. 1B

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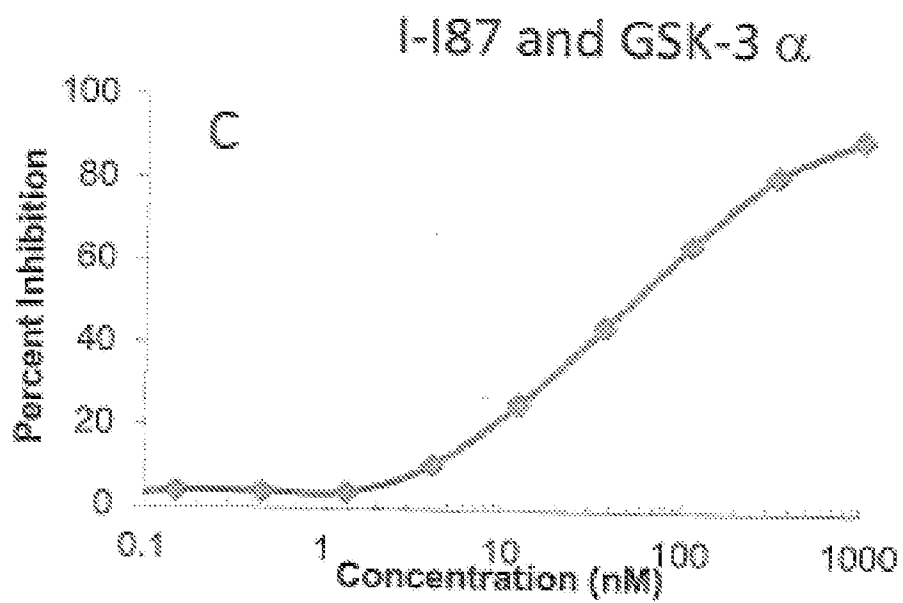


FIG. 2A

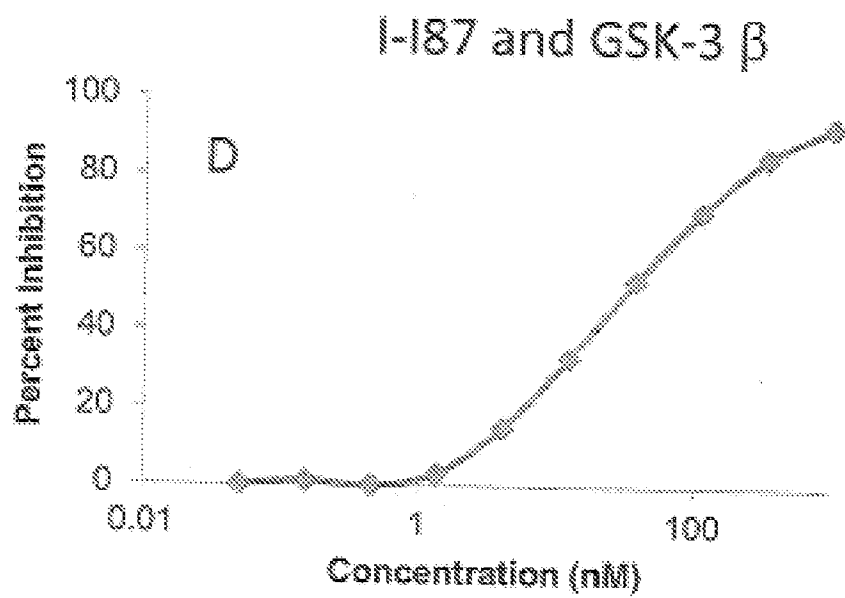


FIG. 2B

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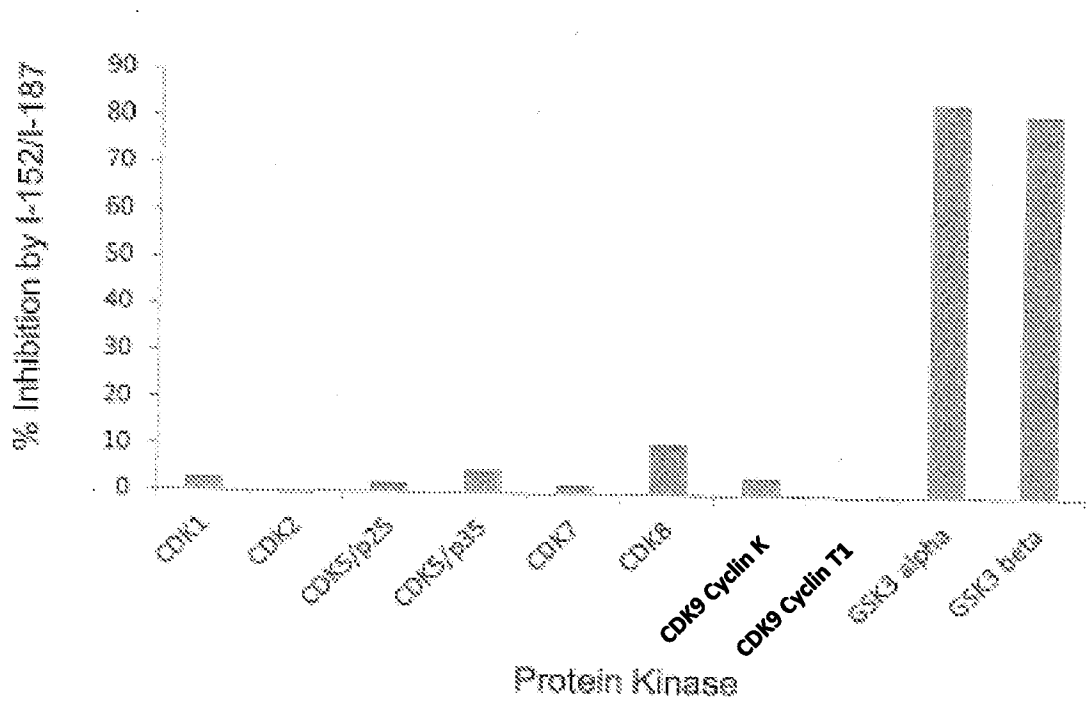


FIG. 3

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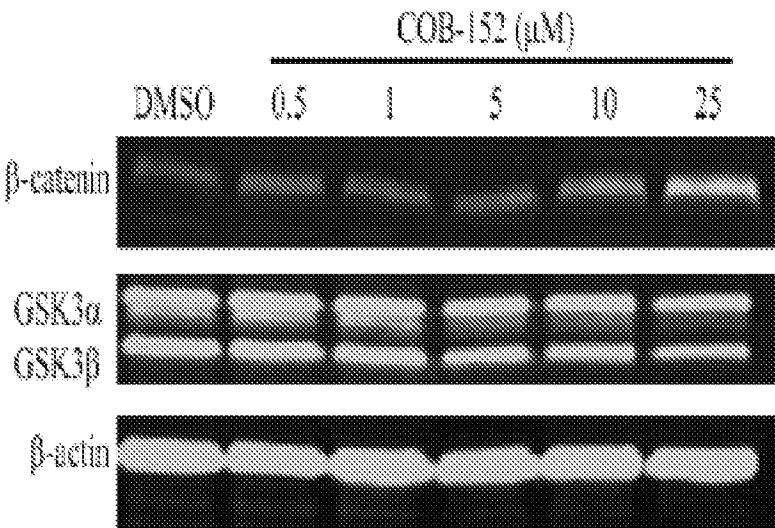


FIG. 4A

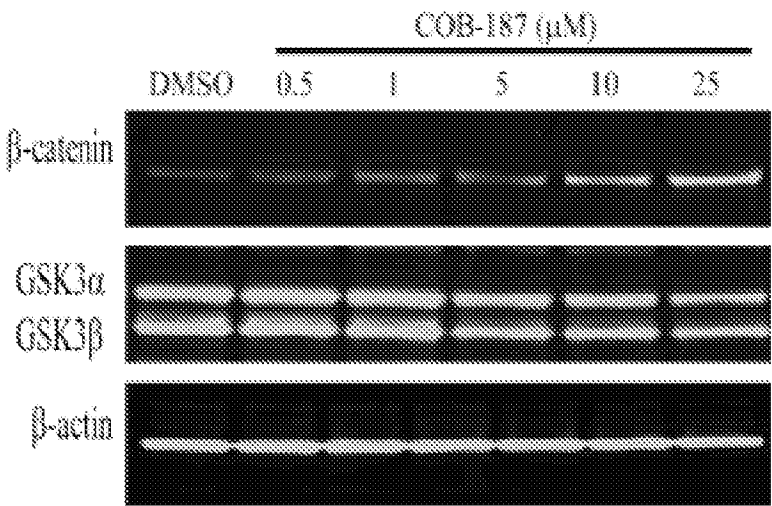


FIG. 4B

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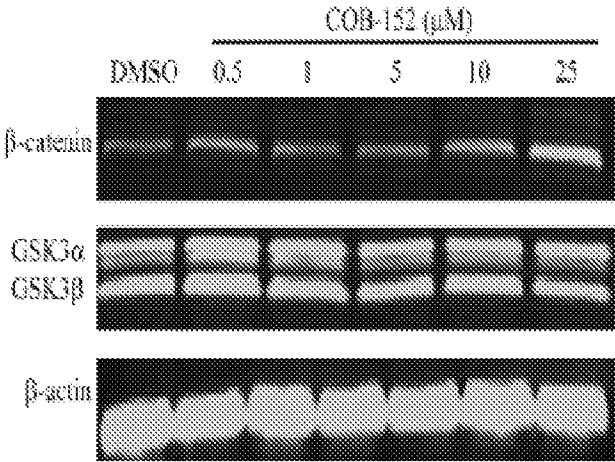


FIG. 5A

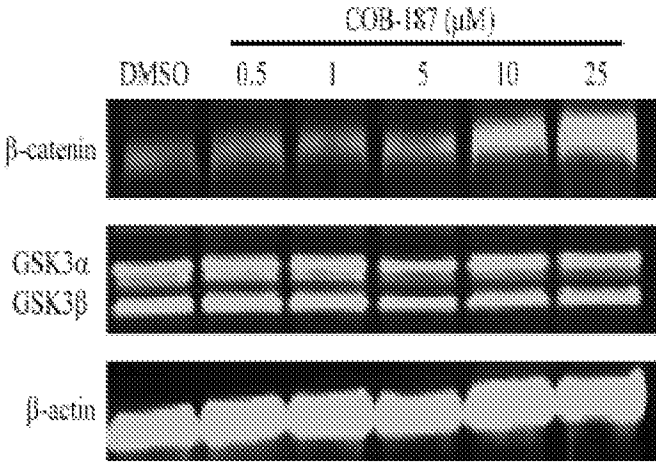


FIG. 5B

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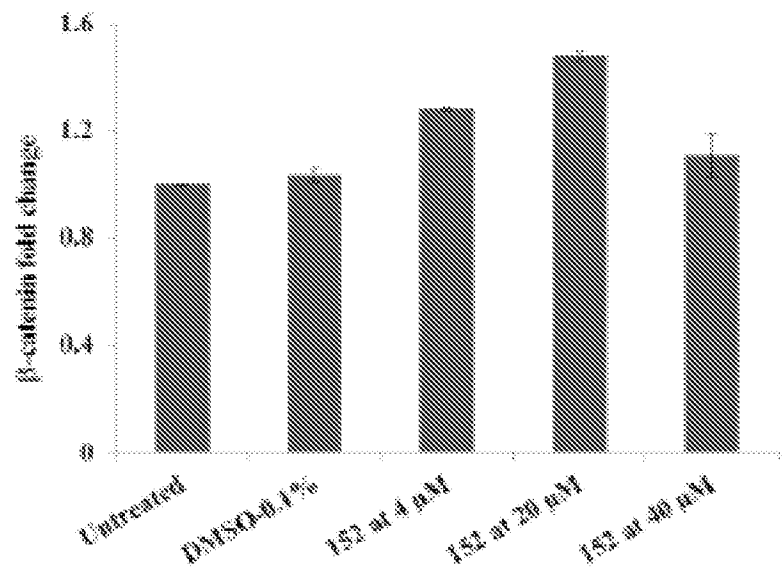


FIG. 6A

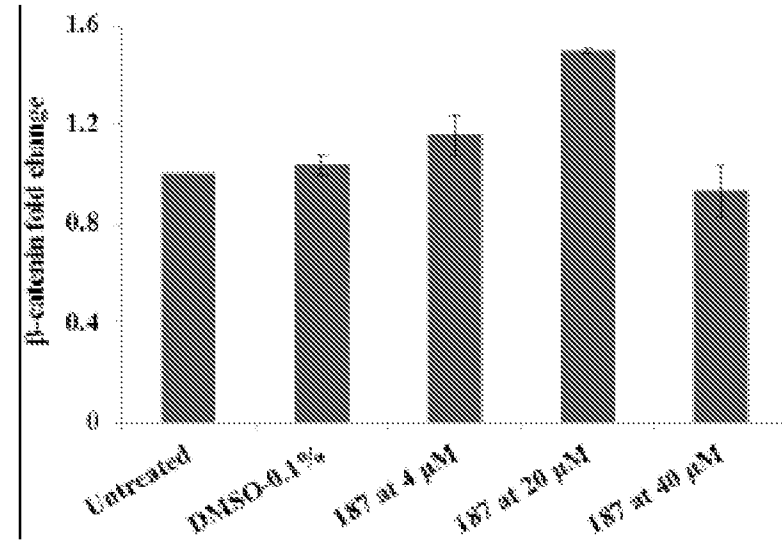


FIG. 6B

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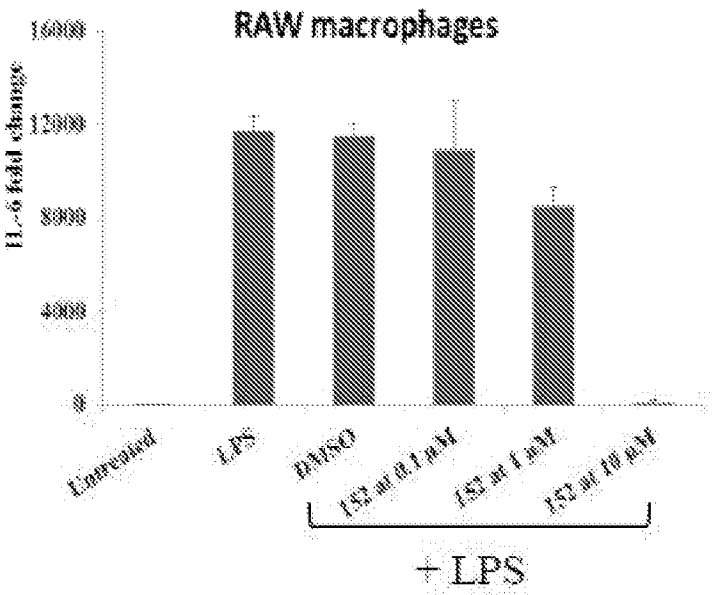


FIG. 7

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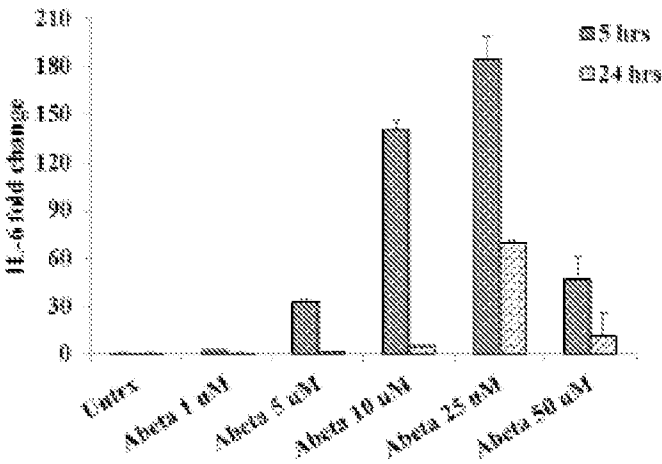


FIG. 8A

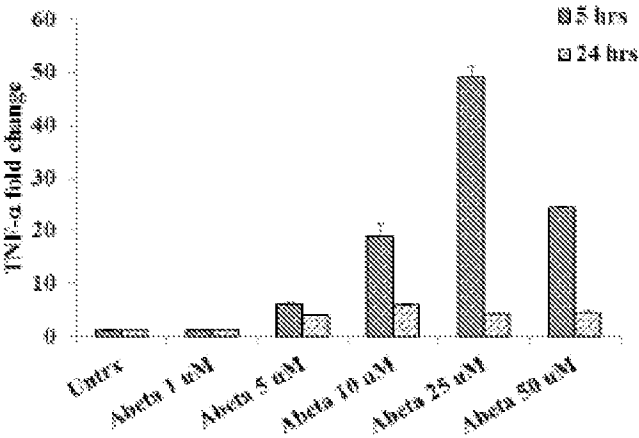


FIG. 8B

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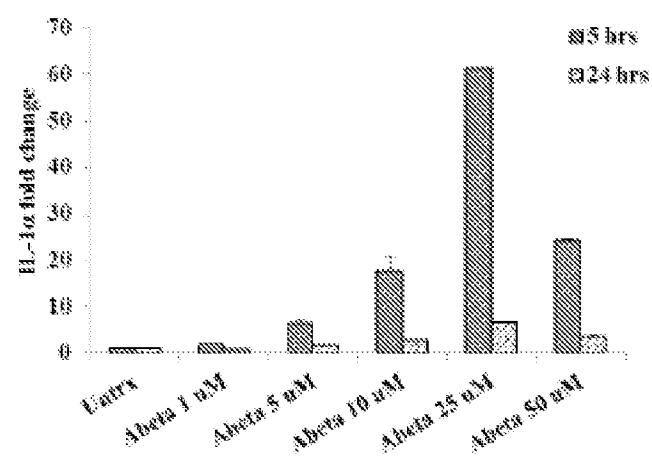


FIG. 8C

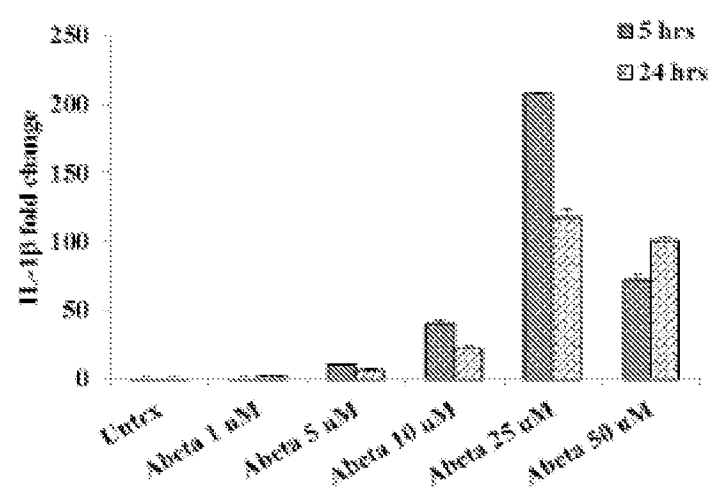


FIG. 8D

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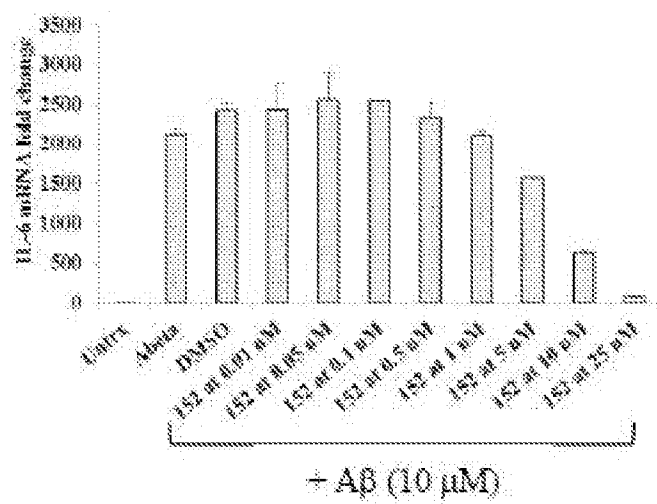


FIG. 9A

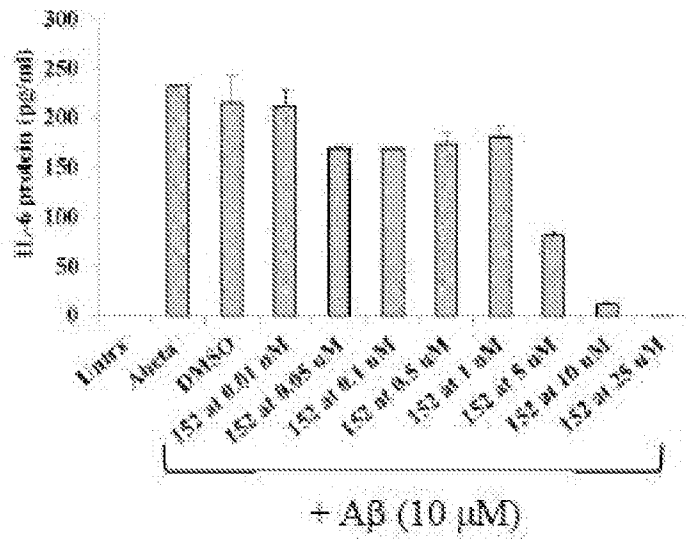


FIG. 9B

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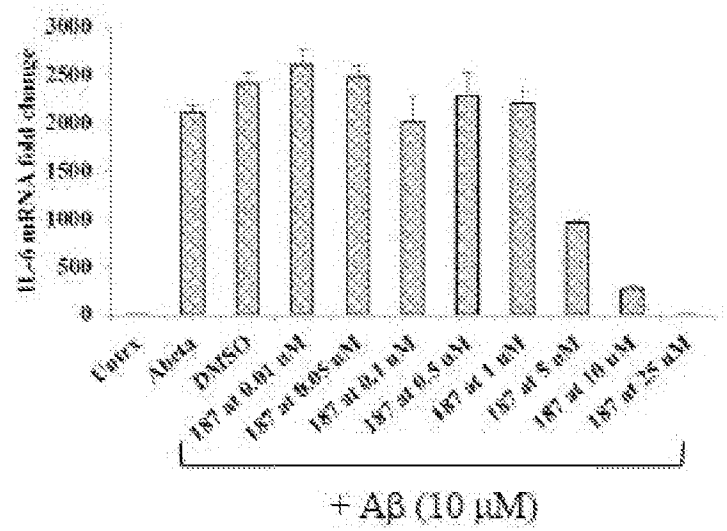


FIG. 9C

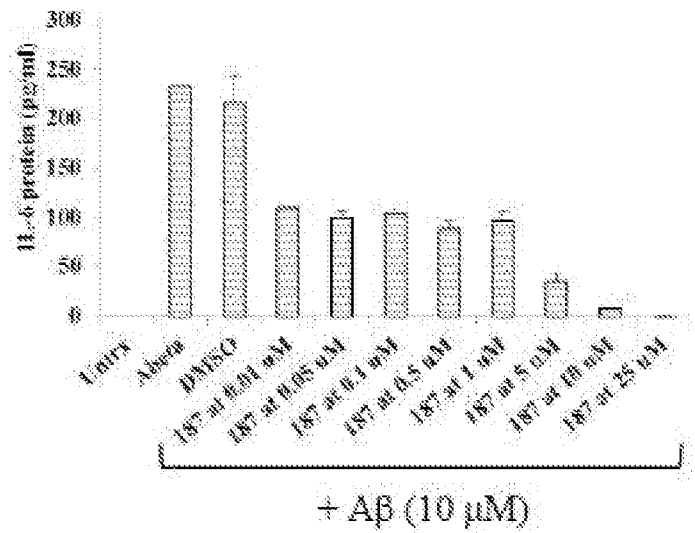


FIG. 9D

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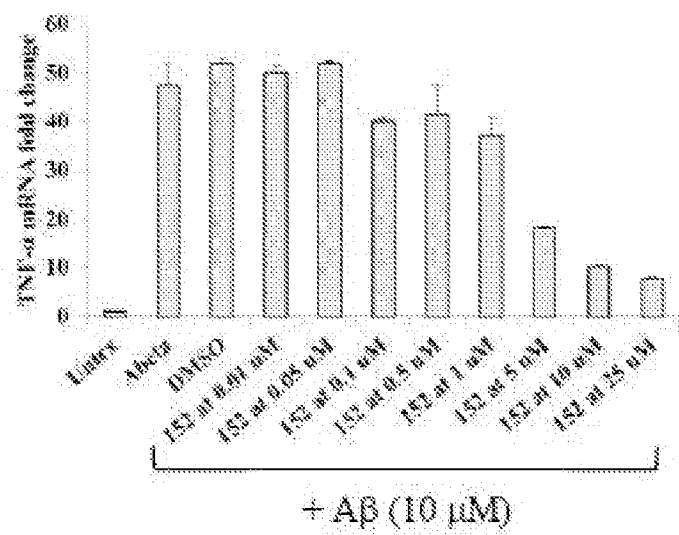


FIG. 10A

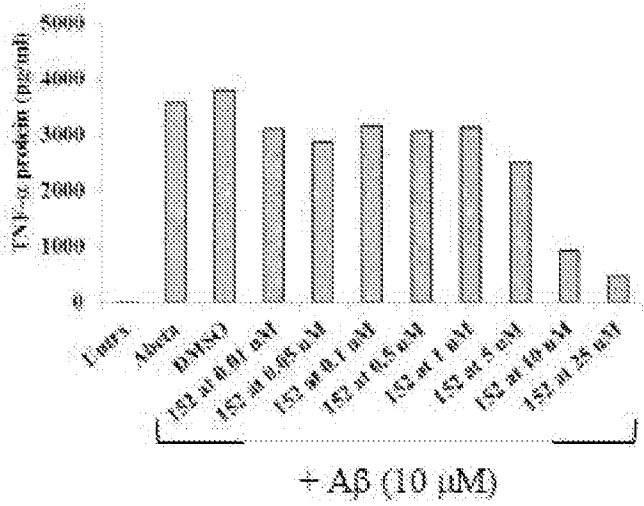


FIG. 10B

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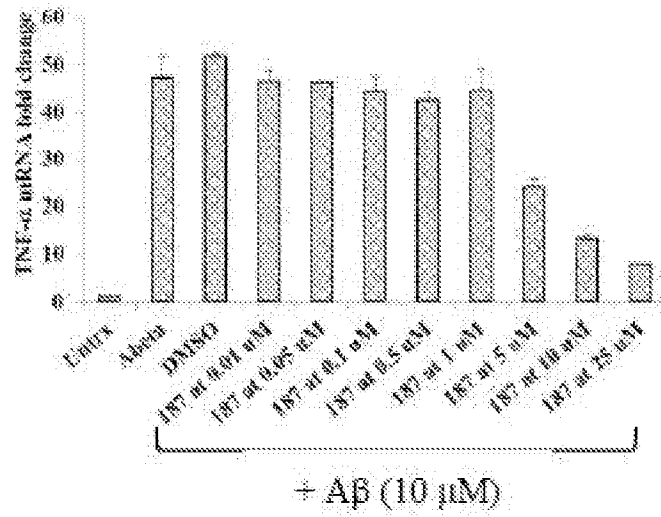


FIG. 10C

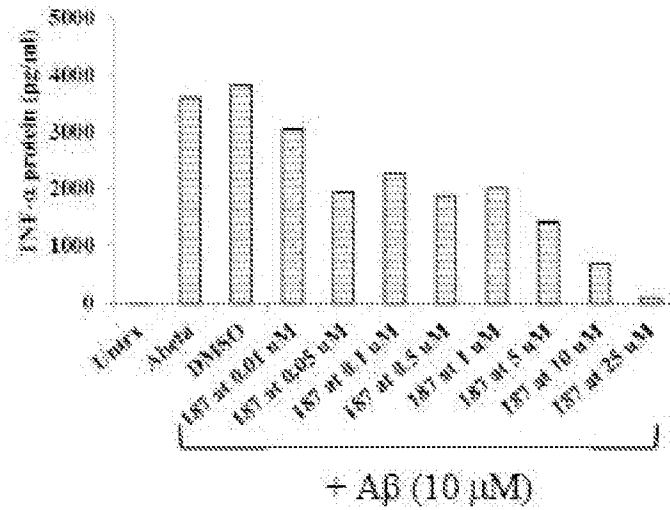


FIG. 10D

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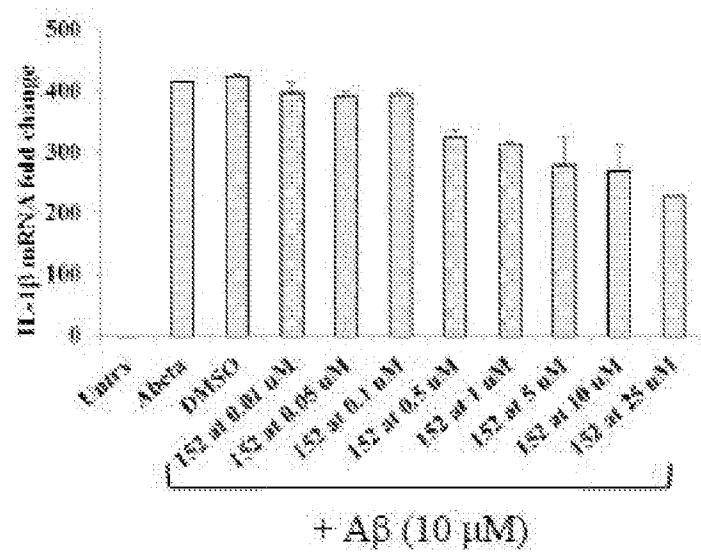


FIG. 11A

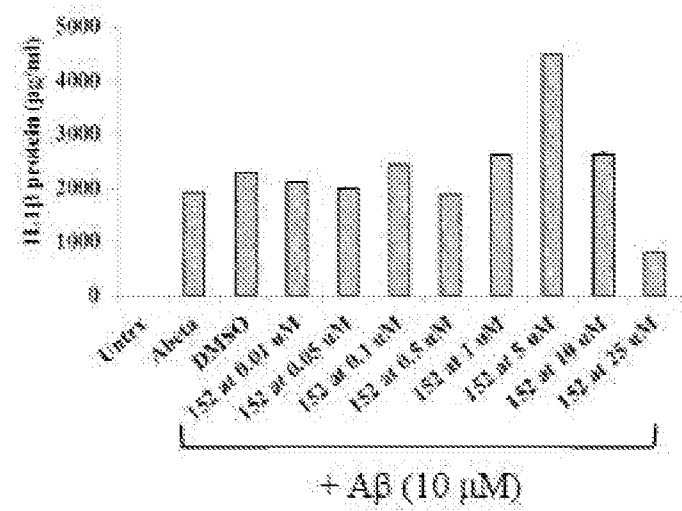


FIG. 11B

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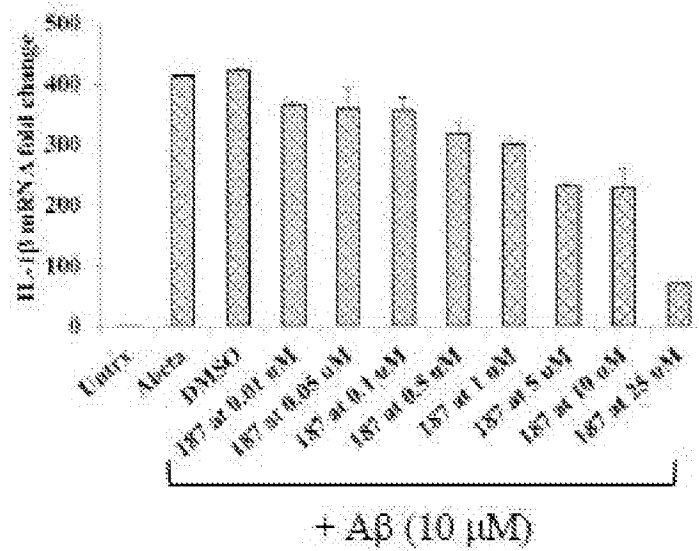


FIG. 11C

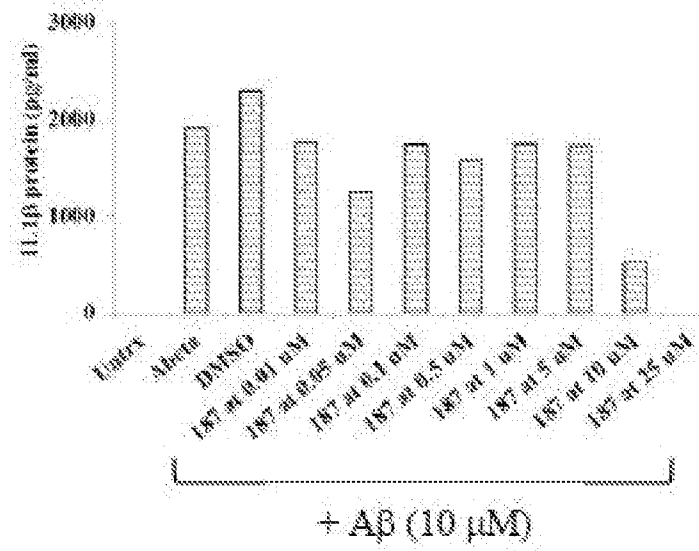


FIG. 11D

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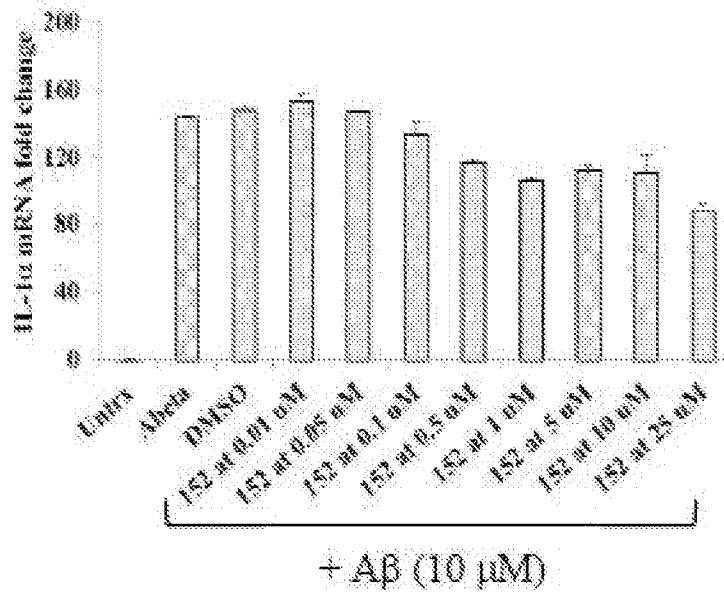


FIG. 12A

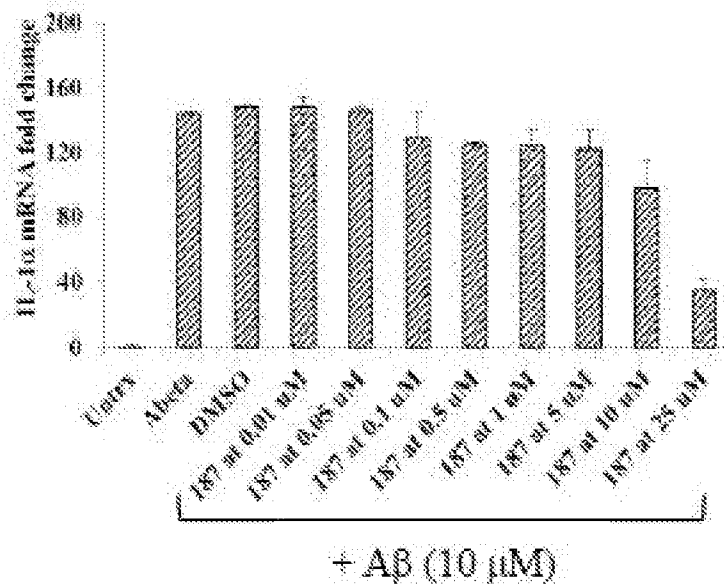


FIG. 12B

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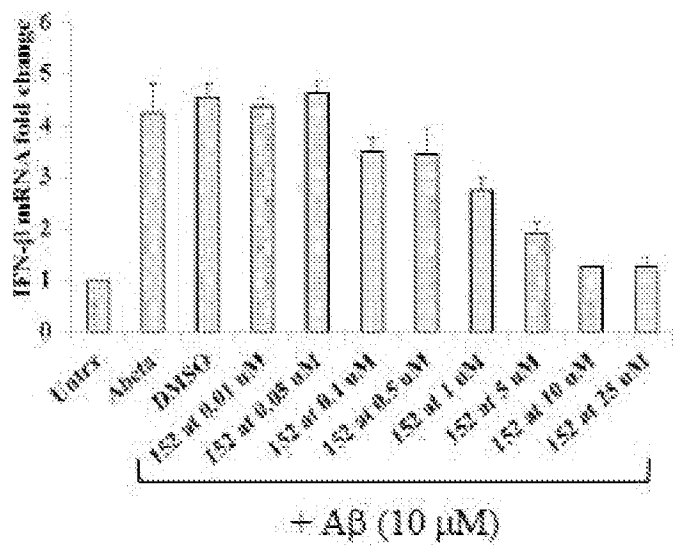


FIG. 13A

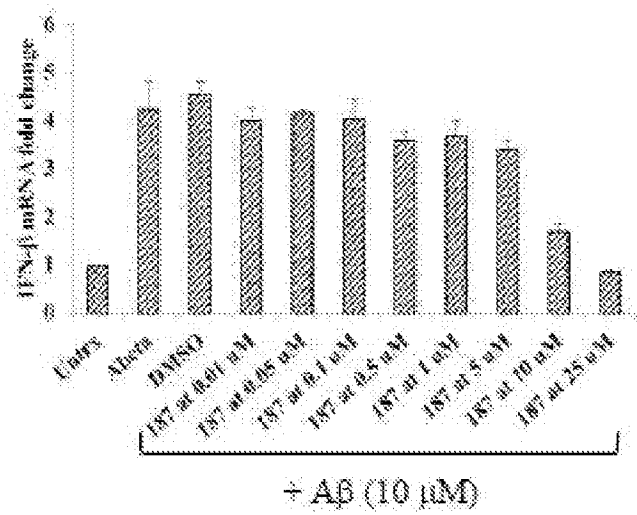


FIG. 13B

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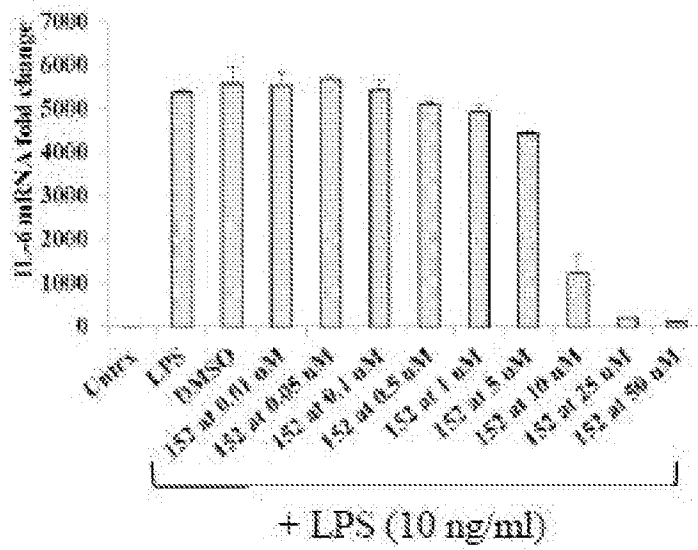


FIG. 14A

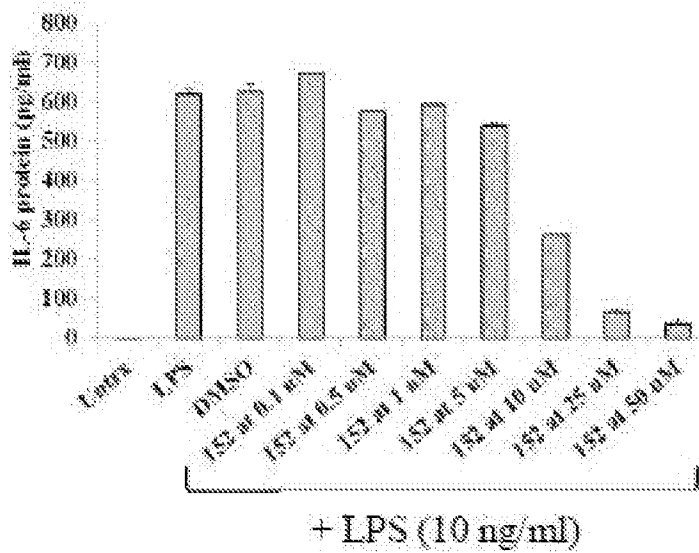


FIG. 14B

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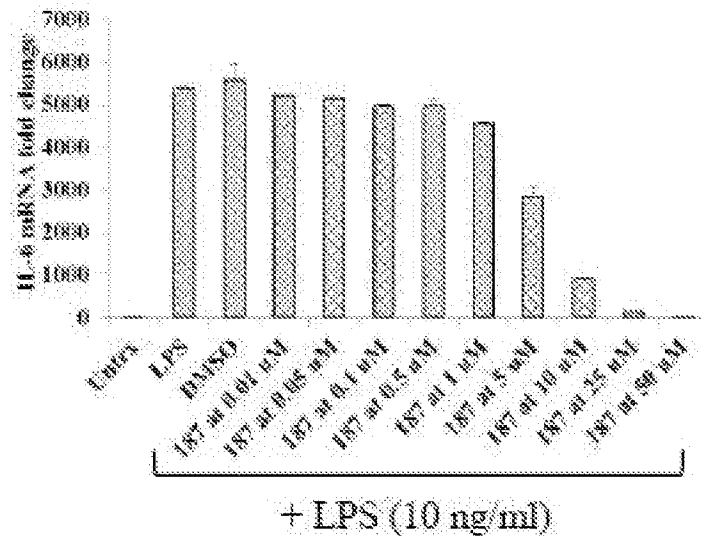


FIG. 14C

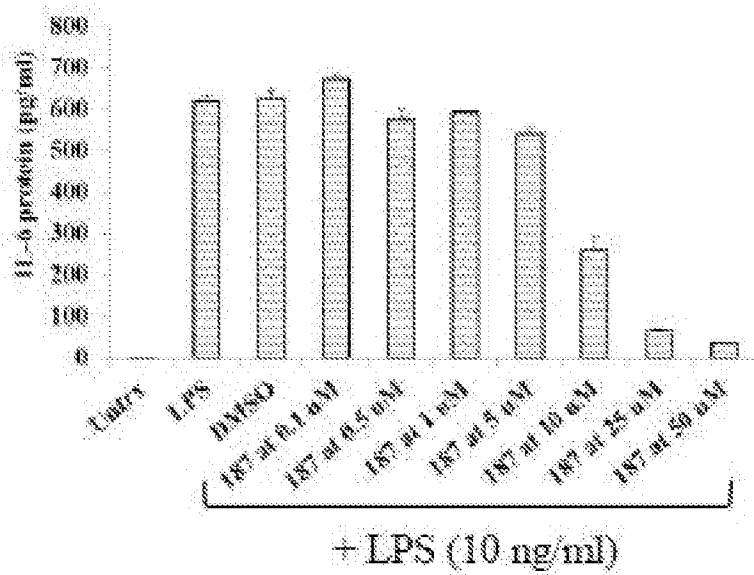


FIG. 14D

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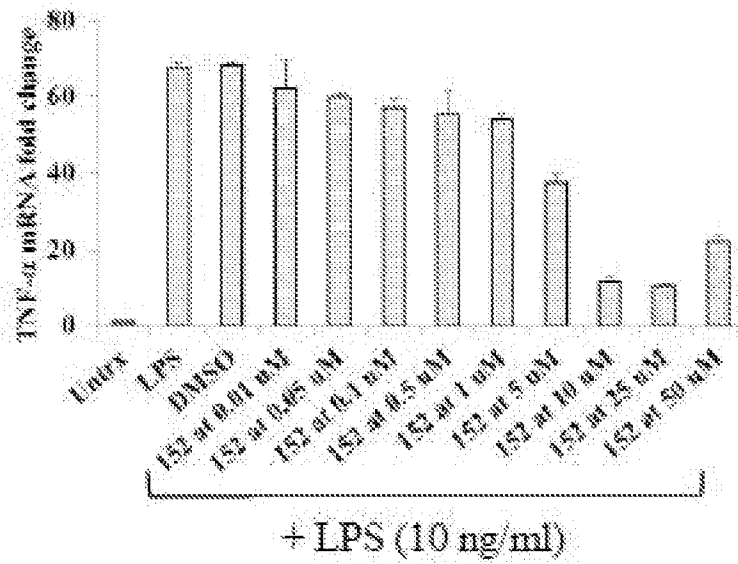


FIG. 15A

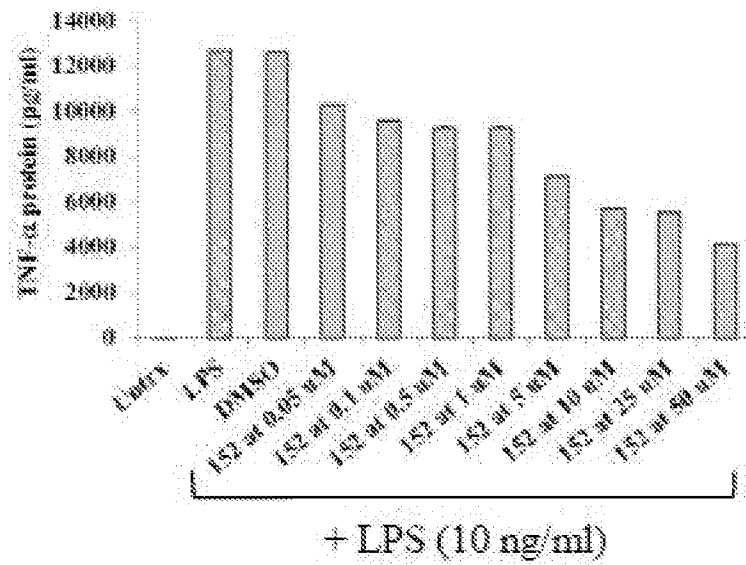


FIG. 15B

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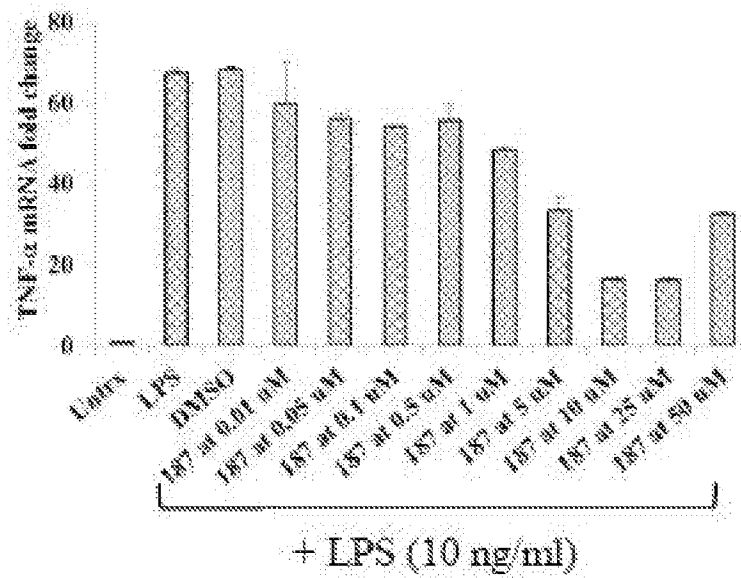


FIG. 15C

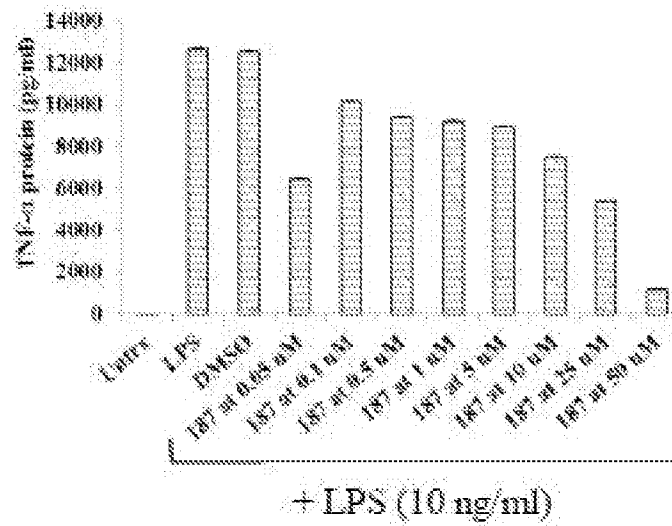


FIG. 15D

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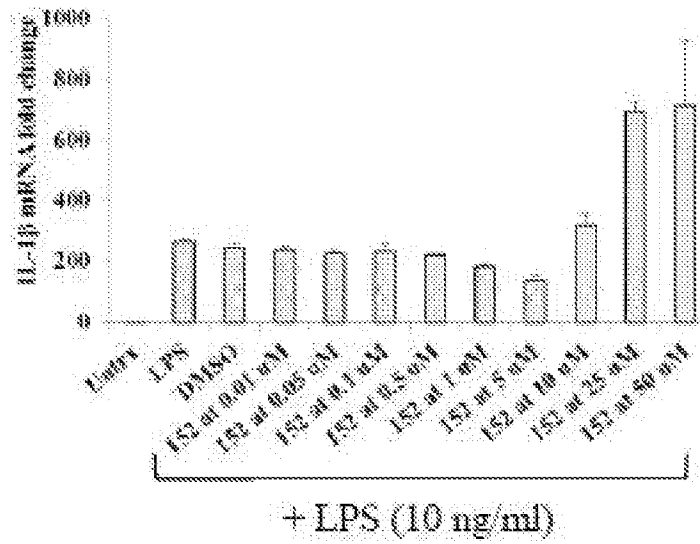


FIG. 16A

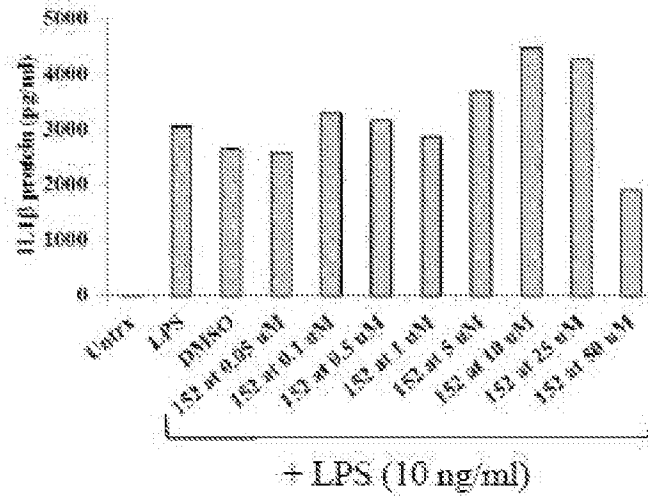


FIG. 16B

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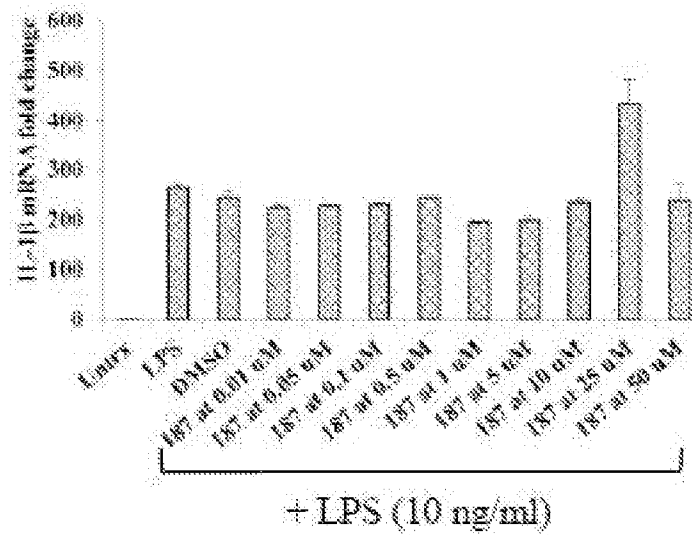


FIG. 16C

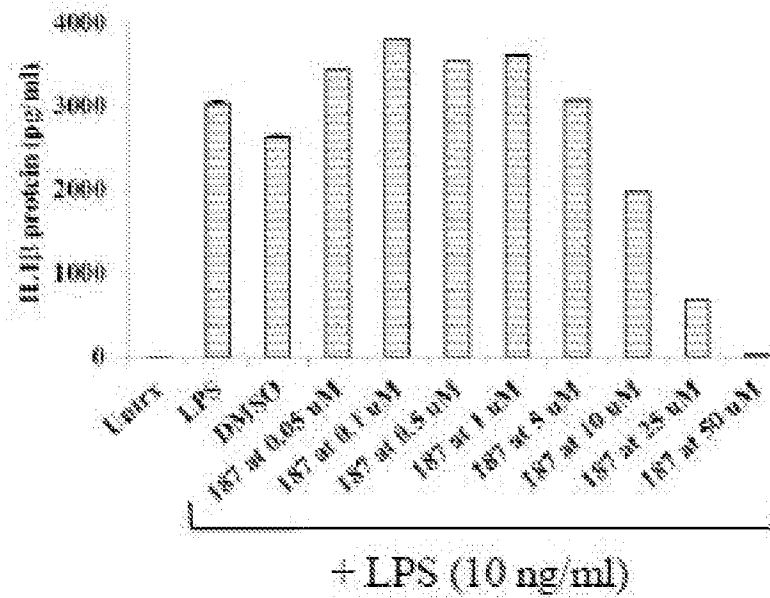


FIG. 16D

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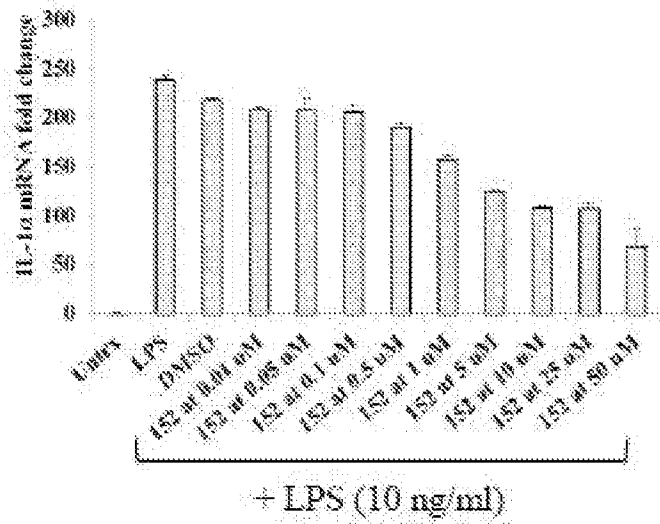


FIG. 17A

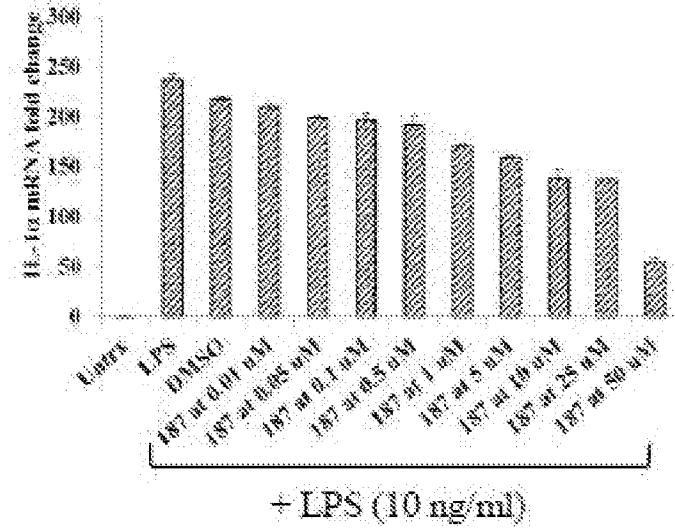


FIG. 17B

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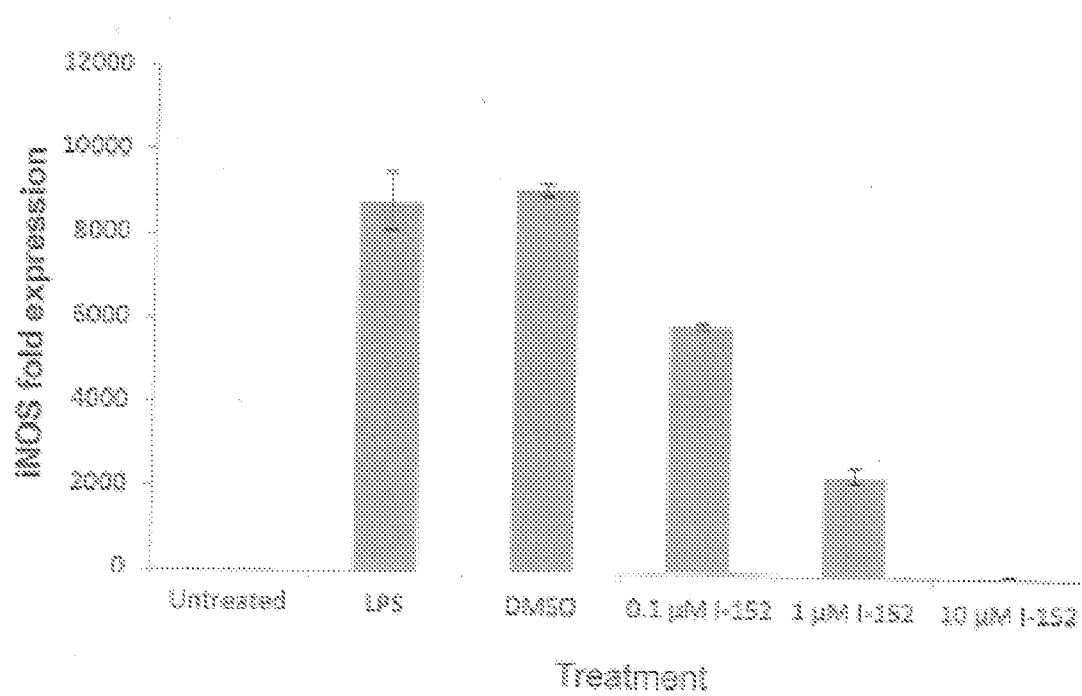


FIG. 18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/029505

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/41 (2015.01)

CPC - A61K 31/41 (2015.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/41, 31/4164, 31/4168; A61P 35/00, 43/00 (2015.01)

CPC - A61K 31/00, 31/41, 31/4166, 31/4168, 31/426 (2015.05) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 514/392; 548/322.1, 331.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, Google Patents, Google Scholar, PubChem

Search terms used: imidazole 2 thione GSK-3 leukemia pancreatic multiple myeloma glioblastoma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0283303 A1 (PANNECOUQUE et al) 08 November 2012 (08.11.2012) entire document	1-10, 13-17, 25, 27, 29, 30, 33-35, 38, 39, 44
Y		11, 12, 18-23, 26, 28, 31, 32, 36, 37, 40-42, 45, 47
Y	US 2010/004304 A1 (KOHN et al) 07 January 2010 (07.01.2010) entire document	11, 31, 32, 36
Y	US 2005/0277678 A1 (LOHRAY et al) 15 December 2005 (15.12.2005) entire document	12, 26
Y	EMAMI et al. Synthesis and Evaluation of 2(3H)-Thiazole Thiones as Tyrosinase Inhibitors. Arch. Pharm. Chem. Life Sci. 345(8), 629-637, 2012. [retrieved on 07 July 2015]. Retrieved from the Internet. <URL: http://onlinelibrary.wiley.com/doi/10.1002/ardp.201200028/abstract > entire document	18-23, 28, 40-42, 45, 47
Y	US 2012/0136035 A1 (GIL) 31 May 2012 (31.05.2012) entire document	37

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 July 2015

Date of mailing of the international search report

22 JUL 2015

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